



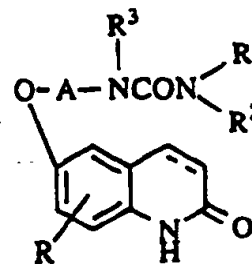
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(54) Title: CARBOSTYRIL DERIVATIVES AS ANTITHROMBOTIC AGENTS

(57) Abstract

A carbostyryl derivative of formula (1), wherein A is lower alkylene, R is H, halogen or lower alkoxy, R¹ and R² are each lower alkyl being optionally substituted by OH, lower alkoxy, phenyl-lower alkoxy or lower alkanoyloxy; cycloalkyl being optionally substituted by OH, hydroxy-lower alkoxy or lower alkanoyloxy; or amino being optionally substituted by lower alkyl or cycloalkyl, R³ is H, lower alkyl, lower alkenyl or hydroxy-lower alkyl, and the bond between 3- and 4-positions of the carbostyryl nucleus is single or double, provided that when R and R³ are H, R¹ and R² should not be either unsubstituted lower alkyl or unsubstituted cycloalkyl, or a salt thereof, which shows antithrombotic activities, intima thickening inhibitory activity, the platelet mass dissociating activity and increasing activity of the blood flow in the brain and the peripheral vessel, and hence, is useful as medicines in the prophylaxis or treatment of various ischemic diseases.



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DESCRIPTION

CARBOSTYRIL DERIVATIVES AS ANTITHROMBOTIC AGENTS

5 Technical Field

The invention relates to novel carbostyryl derivatives being useful as medicines in the prophylaxis or treatment of various ischemic diseases.

Background Art

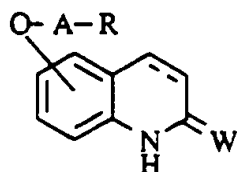
Ischemic diseases such as thrombosis or arteriosclerosis may break out
10 and become worse by a complicated interaction of three factors of the change
in the components in the blood fluid, the abnormal blood flow and the disorder
of the blood vessel wall. Although thrombosis is caused by various factors, it
mainly breaks out by the disorder of the intima cells like in the case of
atherosclerosis, subsequently the activation of platelets, and then by the
15 adhesion and aggregation of platelets.

Arteriosclerosis breaks out and becomes worse by the growth of the
blood vessel smooth muscle cells by the complicated interaction of the above
mentioned three factors, and then by the thickening of the intima.

Thus, it is very important that a medicant being useful in the prophylaxis
20 or treatment of ischemic diseases such as thrombosis or arteriosclerosis should
essentially show both antithrombotic activity and intima thickening inhibitory
activity.

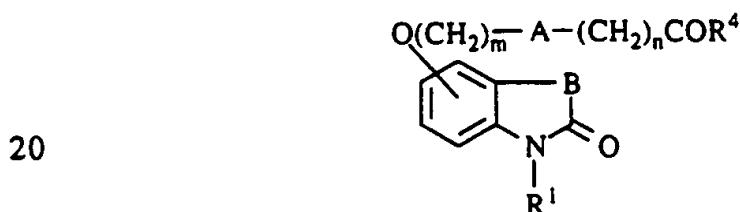
There are known various carbostyryl derivatives. For example, WO
93/04042 (= JP-A-5-194405) discloses carbostyryl derivatives of the formula:

2



wherein A is a lower alkylene; R is $-NR^1R^2$, $-SO_2NR^3R^4$, or $-Y-NR^5R^6$; R¹ is
 5 $-(CO)_l-B-(CO)_m-NR^7R^8$ or $-SO_2-D-R^9$; R² is H, a cycloalkyl, a substituted or
 unsubstituted phenyl, etc.; or R¹ and R² may combine with the adjacent
 nitrogen to form a substituted or unsubstituted pyrrolidinyl; R³ is H, lower alkyl,
 $-E-(CO)_n-NR^{10}R^{11}$, etc.; R⁴ is H, a cycloalkyl, a substituted or unsubstituted
 phenyl, a heterocyclic group-substituted alkyl, etc.; Y is $-NHCO-$, $-NHC(=S)-$
 10 or $-C(=S)-$; R⁵ and R⁶ are each H, a lower alkyl, a cycloalkyl, a piperidinyl-
 alkyl, etc.; and W is O or S, which have a platelet aggregation inhibitory activity
 and a platelet adhesion inhibitory activity. Some compounds inclusive in the
 general formula of the present invention may fall within the scope of the general
 formula of this prior art, and those possibly overlapping compounds are
 15 excluded from the present invention by the proviso phrase.

U.S. Patent 4,070,470, 4,216,220 and 4,313,947 disclose carbostyryl
 derivatives of the formula:

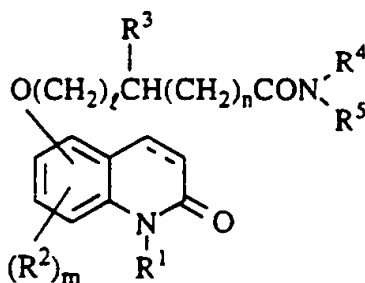


wherein R¹ is H, lower alkyl, lower alkenyl or aralkyl, R⁴ is OH, alkoxy,
 substituted or unsubstituted amino, heterocyclic amino, etc., A is lower alkylene

or vinylene, B is $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$ or $-\text{CH}=\text{CH}-$, and m and n are 0 or a positive integer with m+n being no more than 11, which have a platelet aggregation inhibitory activity.

U.S. Patent 4,298,739 discloses carbostyryl derivatives of the formula:

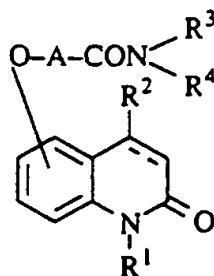
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10 wherein R^1 is H, lower alkyl, lower alkenyl or phenylalkyl, R^2 is H, halogen, OH or phenylalkoxy, R^3 is H, OH or lower alkyl, R^4 is cycloalkyl, substituted or unsubstituted phenyl, cycloalkylalkyl, etc., R^5 is H, alkyl, lower alkenyl, phenyl, cycloalkyl, etc., m is 1-3, and ℓ and n are 0 or an integer of 1-7, which have a platelet aggregation inhibitory activity.

15

U.S. Patent 4,435,404 discloses carbostyryl derivatives of the formula:



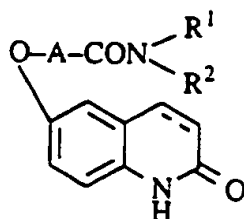
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wherein R^1 is H, R^2 is H or lower alkyl, R^3 is hydroxy-lower alkyl having 1 to 3 hydroxy groups, lower alkanoyloxy-lower alkyl, etc., R^4 is cycloalkyl having 1 to 3 hydroxy groups, etc., or R^3 and R^4 form a group of the formula:

—N—N—R³ (R³ is phenyl, etc.), A is lower alkylene, which have a platelet aggregation inhibitory activity.

EP-A-0450066 (published on October 9, 1989) discloses carbostyryl derivatives of the formula:

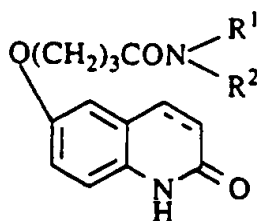
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wherein R¹ is substituted or unsubstituted cycloalkyl-lower alkyl, cycloalkyl, substituted or unsubstituted phenyl, piperidinyl-lower alkyl, etc., R² is substituted or unsubstituted heterocyclo-lower alkyl, pyridylthio-lower alkyl, substituted or unsubstituted lower alkyl, etc., and A is an alkylene, which have a platelet aggregation inhibitory activity.

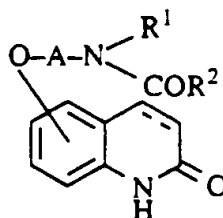
JP-A-55-79371 (published on June 14, 1980) discloses carbostyryl derivatives of the formula:

15



wherein R¹ is lower alkyl, R² is oxo-substituted cycloalkyl, which have a platelet aggregation inhibitory activity.

JP-A-57-14574 (published on January 25, 1982) discloses carbostyryl derivatives of the formula:



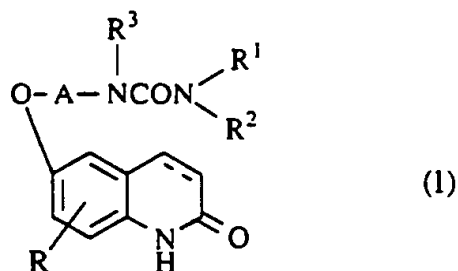
- 5 wherein R^1 is lower alkyl, R^2 is cycloalkyl or pyridyl, and A is an alkylene, which have a platelet aggregation inhibitory activity.

There are many other literatures which disclose carbostyryl derivatives analogous to the compounds of the present invention.

- 10 However, those carbostyryl derivatives of those known literatures as mentioned above are distinguished from the compounds of the present invention in that those known compounds other than those of the above first literature WO 93/04042 have no ureido-lower alkoxy substituent on the carbostyryl nucleus.

Disclosure of the Invention

- 15 The present invention relates to a novel carbostyryl derivative of the following formula (1):



20

wherein A is a lower alkylene group,

R is a hydrogen atom, a halogen atom or a lower alkoxy group,

R^1 and R^2 are the same or different and are each a lower alkyl group

having optionally a substituent selected from a hydroxy group, a lower alkoxy group, a phenyl-lower alkoxy group and a lower alkanoyloxy group; a cycloalkyl group having optionally a substituent selected from a hydroxy group, a hydroxy-substituted lower alkoxy group and a lower alkanoyloxy group; or an amino group having optionally a substituent selected from a lower alkyl group and a cycloalkyl group,

R³ is a hydrogen atom, a lower alkyl group, a lower alkenyl group or a hydroxy-substituted lower alkyl group, and

the bond between 3- and 4-positions of the carbostyryl nucleus is a single bond or a double bond,

provided that when R and R³ are a hydrogen atom, R¹ and R² should not be either an unsubstituted lower alkyl group or an unsubstituted cycloalkyl group, or a salt thereof.

According to the studies of the present inventors, the carbostyryl derivatives (1) of the present invention and a salt thereof show both potent antithrombotic activity and intima thickening inhibitory activity *in vivo*, and they also show a platelet aggregation inhibitory activity, a dissociation activity of platelet mass, and an increasing activity in blood flow in the brain and the peripheral vessel, etc.

The present compounds show the pharmacological activities for a prolonged time, and show very weak effects on the circulation, e.g. very weak increasing activity in heart beat, very weak hypotensive activity, etc., and hence, they show very few side effects, especially on the heart. Besides, the

present compounds are well absorbed at the digestion organs and show excellent efficiency of migration into the blood flow.

Thus, the present compounds are useful in the prophylaxis or treatment of thrombotic diseases or arteriosclerotic diseases. For example, the present
5 compounds may clinically be used in the prophylaxis or treatment of various ischemic diseases, for example, in the prophylaxis or treatment of brain diseases such as cerebral atherosclerosis, cerebral infarction, transient cerebral ischemic attack (TIA), reversible ischemic neurological deficit (RIND), etc., heart diseases such as myocardial infarction, angina pectoris, etc., chronic arterial embolisms
10 such as Buerger disease (thromboangiitis obliterans), embolic atherosclerosis, intermittent claudication, etc., diabetic complications such as diabetic neuropathy, diabetic dermopathy, diabetic nephropathy, etc., in the prevention of re-stenosis after interventional treatment of percutaneous transluminal coronary angioplasty (PTCA), directional coronary atherectomy (DCA), stent,
15 etc., in the prevention of re-occlusion after the transplant of artificial organs such as artificial blood vessel or kidney, in the prevention of thrombosis or embolism during the extracorporeal circulation such as artificial kidney dialysis or operations.

Besides, the present compounds also show a potent inhibitory activity
20 against cGMP inhibited cAMP PDE (PDE 3) which is classified by phosphodiesterase nomenclature disclosed in Molecular Pharmacology, 46, pp. 399-405 (1994).

The cyclic adenosine monophosphate (cAMP) is a representative intracellular second messenger in the living body, and decomposed and

inactivated by phosphodiesterase (hereinafter, abbreviated as "PDE").

Currently, at least 7 different PDE isozyme gene families are recognized and these PDEs are widely distributed in many cell types and tissues. Thus, a PDE inhibitor increases the concentration of cAMP in tissue cells, and hence, is
5 useful in the prophylaxis or treatment of various diseases caused by the decrease in cAMP level which is induced by the abnormal metabolism of cAMP.

As is disclosed in Pharmacology & Therapeutics, 51, pp. 13-33 (1991), Trends in Pharmacological Science, 11, pp. 150-155 (1990), Trends in Pharmacological Science, 12, pp. 19-27 (1991), the present compounds having a
10 PDE inhibitory activity can also be clinically used in the prophylaxis or treatment of obesity based on the lipocatabolic action in fatty cells, or in the treatment of allergic diseases and asthma based on the inhibitory activity of the release of the chemical mediator from inflammatory cells in addition to the clinical use based on the above mentioned antithrombotic activity and the
15 intima thickening inhibitory activity.

Each group in the above formula (1) specifically includes the following groups.

The "lower alkylene group" includes a straight chain or branched chain alkylene group having 1 to 6 carbon atoms, for example, methylene, ethylene,
20 methylmethylene, trimethylene, 2-methyltrimethylene, 2,2-dimethyltrimethylene, tetramethylene, pentamethylene, hexamethylene, 2-ethyltrimethylene, 1-methyltrimethylene, and the like.

The "lower alkanoyloxy group" includes a straight chain or branched chain alkanoyloxy group having 2 to 6 carbon atoms, for example, acetyloxy,

propionyloxy, butyryloxy, isobutyryloxy, pentanoyloxy, t-butylcarbonyloxy, hexanoyloxy, and the like.

The "lower alkyl group having optionally a substituent selected from a hydroxy group, a lower alkoxy group, a phenyl-lower alkoxy group and a lower alkanoyloxy group" includes a straight chain or branched chain alkyl group having 1 to 6 carbon atoms which may optionally have 1 to 3 substituents selected from a hydroxy group, a straight chain or branched chain alkoxy group having 1 to 6 carbon atoms, a phenylalkoxy group wherein the alkoxy moiety is a straight chain or branched chain alkoxy group having 1 to 6 carbon atoms, and a straight chain or branched chain alkanoyloxy group having 2 to 6 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, hexyl, 2-hydroxyethyl, 3-hydroxypropyl, 4-hydroxybutyl, 2-hydroxybutyl, 3-hydroxybutyl, 5-hydroxypentyl, 2-hydroxypentyl, 3-hydroxypentyl, 4-hydroxypentyl, 6-hydroxyhexyl, 2-hydroxyhexyl, 3-hydroxyhexyl, 4-hydroxyhexyl, 1-methyl-2-hydroxyethyl, 2-hydroxypropyl, 1,1-dimethyl-2-hydroxyethyl, 1,2-dihydroxyethyl, 2,2-dihydroxyethyl, 1,3-dihydroxypropyl, 2,3-dihydroxypropyl, 1,2,3-trihydroxypropyl, 1,4-dihydroxybutyl, 2,4-dihydroxybutyl, 3,4-dihydroxybutyl, 1,2-dihydroxybutyl, 2,3-dihydroxybutyl, 1,3-dihydroxybutyl, 2,2-dihydroxybutyl, 1,2,3-trihydroxybutyl, 2,3,4-trihydroxybutyl, 2,3-dihydroxypentyl, 3,4-dihydroxypentyl, 3,5-dihydroxypentyl, 2,3,4-trihydroxypentyl, 3,4,5-trihydroxypentyl, 2,4,5-trihydroxypentyl, 2,3-dihydroxyhexyl, 2,5-dihydroxyhexyl, 2,6-dihydroxyhexyl, 3,4-dihydroxyhexyl, 4,5-dihydroxyhexyl, 4,6-dihydroxyhexyl, 5,6-dihydroxyhexyl, 2,3,4-trihydroxyhexyl, 3,4,5-trihydroxyhexyl, 4,5,6-trihydroxyhexyl, 3,4-diacetyloxy-5-hydroxyhexyl,

acetyloxymethyl, 2-acetyloxyethyl, 3-acetyloxypropyl, 2-acetyloxybutyl, 5-propanoyloxypentyl, 6-butyryloxyhexyl, pentanoyloxymethyl, 4-hexanoyloxybutyl, 3,4,5-triacetyloxyhexyl, 2,3-diacetyloxypropyl, 2-ethoxypropyl, 2-benzoyloxypropyl, 2-ethoxybutyl, 2-benzyloxybutyl, 2-methoxyethyl, 4-propoxybutyl, 2-butoxybutyl, 3-pentyloxybutyl, 5-hexyloxypentyl, 2-ethoxypentyl, 3-methoxypentyl, 4-ethoxypentyl, 6-methoxyhexyl, 2-ethoxyhexyl, 3-ethoxyhexyl, 4-methoxyhexyl, 1-methyl-2-ethoxyethyl, 1,1-dimethyl-2-ethoxyethyl, 2,3-diethoxypropyl, 2-(2-phenylethoxy)ethyl, 4-(1-phenylethoxy)butyl, 2-(3-phenylpropoxy)butyl, 3-(4-phenylbutoxy)butyl, 5-(5-phenylpentyloxy)pentyl, 2-(6-phenylhexyloxy)pentyl, 3-benzyloxypentyl, 4-benzyloxypentyl, 6-(2-phenylethoxy)hexyl, 2-(1-phenylethoxy)hexyl, 3-benzyloxyhexyl, 4-benzyloxyhexyl, 1-methyl-2-benzyloxyethyl, 1,1-dimethyl-2-(2-phenylethoxy)ethyl, 2,3-dibenzyloxypropyl, etc.

The "cycloalkyl group having optionally a substituent selected from a hydroxy group, a hydroxy-substituted lower alkoxy group and a lower alkanoyloxy group" includes a cycloalkyl group having 3 to 8 carbon atoms which may optionally have 1 to 3 substituents selected from a hydroxy group, a straight chain or branched chain alkoxy group having 1 to 6 carbon atoms and being substituted by 1 to 3 hydroxy groups, and a straight chain or branched chain alkanoyloxy group having 2 to 6 carbon atoms, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 2-hydroxycyclohexyl, 2-hydroxycyclopropyl, 3-hydroxycyclobutyl, 2-hydroxycyclopentyl, 4-hydroxycycloheptyl, 3-hydroxycyclooctyl, 3-hydroxycyclohexyl, 4-hydroxycyclohexyl, 2,3-dihydroxycyclohexyl, 3,4-dihydroxycyclohexyl, 2,4,6-tri-

hydroxycyclohexyl, 2-propionyloxycyclopropyl, 2-butyryloxycyclobutyl, 3-pentanoyloxycyclopentyl, 3-acetyloxycyclohexyl, 4-acetyloxycyclohexyl, 3-hexanoyloxycycloheptyl, 5-acetyloxycyclooctyl, 2,4-diacetyloxycyclohexyl, 2,3,4-triacetyloxycyclohexyl, 2-hydroxy-4-acetyloxycyclohexyl, 2-(3-hydroxy-
5 propoxy)cyclohexyl, 2-hydroxymethoxycyclopropyl, 3-(2-hydroxyethoxy)-cyclobutyl, 2-(1-hydroxyethoxy)cyclopentyl, 4-(3-hydroxypropoxy)cycloheptyl, 3-(4-hydroxybutoxy)cyclooctyl, 3-(5-hydroxypentyloxy)cyclohexyl, 4-(2-hydroxyethoxy)cyclohexyl, 2,3-di-hydroxymethoxycyclohexyl, 2,3,4-tri-hydroxymethoxycyclohexyl, etc.

10 The "lower alkyl group" includes a straight chain or branched chain alkyl group having 1 to 6 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, hexyl, etc.

 The "lower alkenyl group" includes a straight chain or branched chain alkenyl group having 2 to 6 carbon atoms, for example, vinyl, allyl, 2-butenyl, 3-
15 butenyl, 1-methylallyl, 2-pentenyl, 2-hexenyl, etc.

 The "lower alkoxy group" includes a straight chain or branched chain alkoxy group having 1 to 6 carbon atoms, for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, pentyloxy, hexyloxy, etc.

 The "phenyl-lower alkoxy group" includes a phenyl-alkoxy group
20 wherein the alkoxy moiety is a straight chain or branched chain alkoxy group having 1 to 6 carbon atoms, for example, benzyloxy, 1-phenylethoxy, 2-phenylethoxy, 3-phenylpropoxy, 4-phenylbutoxy, 5-phenylpentyloxy, 6-phenylhexyloxy, 1,1-dimethyl-2-phenylethoxy, 2-methyl-3-phenylpropoxy, etc.

 The "hydroxy-substituted lower alkyl group" includes a straight chain

or branched chain alkyl group having 1 to 6 carbon atoms and being substituted by 1 to 3 hydroxy groups, for example, hydroxymethyl, 2-hydroxyethyl, 3-hydroxypropyl, 4-hydroxybutyl, 2-hydroxybutyl, 3-hydroxybutyl, 5-hydroxypentyl, 2-hydroxypentyl, 3-hydroxypentyl, 4-hydroxypentyl, 6-hydroxyhexyl, 2-hydroxyhexyl, 3-hydroxyhexyl, 4-hydroxyhexyl, 1-methyl-2-hydroxyethyl, 2-hydroxypropyl, 1,1-dimethyl-2-hydroxyethyl, 1,2-dihydroxyethyl, 2,2-dihydroxyethyl, 1,3-dihydroxypropyl, 2,3-dihydroxypropyl, 1,2,3-trihydroxypropyl, 1,4-dihydroxybutyl, 2,4-dihydroxybutyl, 3,4-dihydroxybutyl, 1,2-dihydroxybutyl, 2,3-dihydroxybutyl, 1,3-dihydroxybutyl, 2,2-dihydroxybutyl, 1,2,3-trihydroxybutyl, 2,3,4-trihydroxybutyl, 2,3-dihydroxypentyl, 3,4-dihydroxypentyl, 3,5-dihydroxypentyl, 2,3,4-trihydroxypentyl, 3,4,5-trihydroxypentyl, 2,4,5-trihydroxypentyl, 2,3-dihydroxyhexyl, 2,5-dihydroxyhexyl, 2,6-dihydroxyhexyl, 3,4-dihydroxyhexyl, 4,5-dihydroxyhexyl, 4,6-dihydroxyhexyl, 5,6-dihydroxyhexyl, 2,3,4-trihydroxyhexyl, 3,4,5-trihydroxyhexyl, 4,5,6-trihydroxyhexyl, etc.

The "halogen atom" is fluorine atom, chlorine atom, bromine atom, and iodine atom.

The "amino group having optionally a substituent selected from a lower alkyl group and a cycloalkyl group" includes an amino group having optionally 1 to 2 substituents selected from a straight chain or branched chain alkyl group having 1 to 6 carbon atoms and a cycloalkyl group having 3 to 8 carbon atoms, for example, amino, methylamino, ethylamino, propylamino, isopropylamino, butylamino, t-butylamino, pentylamino, hexylamino, dimethylamino, diethylamino, dipropylamino, dibutylamino, dipentylamino, dihexylamino,

N-methyl-N-ethylamino, N-ethyl-N-propylamino, N-methyl-N-butylamino, N-methyl-N-hexylamino, cyclopropylamino, cyclobutylamino, cyclopentylamino, cyclohexylamino, cycloheptylamino, cyclooctylamino, N-cyclopropyl-N-cyclohexylamino, N-methyl-N-cyclohexylamino, N-methyl-N-cyclooctylamino, etc.

- 5 The "hydroxy-substituted lower alkoxy group" includes a straight chain or branched chain alkoxy group having 1 to 6 carbon atoms and being substituted by 1 to 3 hydroxy groups, for example, hydroxymethoxy, 2-hydroxyethoxy, 3-hydroxypropoxy, 4-hydroxybutoxy, 2-hydroxybutoxy, 3-hydroxybutoxy, 5-hydroxypentyloxy, 2-hydroxypentyloxy, 3-hydroxypentyl-
 10 oxy, 4-hydroxypentyloxy, 6-hydroxyhexyloxy, 2-hydroxyhexyloxy, 3-hydroxyhexyloxy, 4-hydroxyhexyloxy, 1-methyl-2-hydroxyethoxy, 2-hydroxypropoxy, 1,1-dimethyl-2-hydroxyethoxy, 1,2-dihydroxyethoxy, 2,2-dihydroxyethoxy, 1,3-dihydroxypropoxy, 2,3-dihydroxypropoxy, 1,2,3-trihydroxypropoxy, 1,4-dihydroxybutoxy, 2,4-dihydroxybutoxy, 3,4-dihydroxybutoxy,
 15 1,2-dihydroxybutoxy, 2,3-dihydroxybutoxy, 1,3-dihydroxybutoxy, 2,2-dihydroxybutoxy, 1,2,3-trihydroxybutoxy, 2,3,4-trihydroxybutoxy, 2,3-dihydroxypentyloxy, 3,4-dihydroxypentyloxy, 3,5-dihydroxypentyloxy, 2,3,4-trihydroxypentyloxy, 3,4,5-trihydroxypentyloxy, 2,4,5-trihydroxypentyloxy, 2,3-dihydroxyhexyloxy, 2,5-dihydroxyhexyloxy, 2,6-dihydroxyhexyloxy, 3,4-dihydroxyhexyloxy, 4,5-dihydroxyhexyloxy, 4,6-dihydroxyhexyloxy, 5,6-dihydroxyhexyloxy, 2,3,4-trihydroxyhexyloxy, 3,4,5-trihydroxyhexyloxy, 4,5,6-trihydroxyhexyloxy, etc.

The present invention especially includes the following compounds:

- (1) The carbostyryl derivative of the formula (1) wherein R¹ and R² are a

lower alkyl group having optionally a substituent selected from a hydroxy group, a lower alkoxy group, a phenyl-lower alkoxy group and a lower alkanoyloxy group, R^3 is a hydrogen atom and A is a lower alkylene group, or a salt thereof.

- 5 (2) The carbostyryl derivative of the formula (1) wherein R^1 is a lower alkyl group having optionally a substituent selected from a hydroxy group, a lower alkoxy group, a phenyl-lower alkoxy group and a lower alkanoyloxy group, R^2 is a cycloalkyl group having optionally a substituent selected from a hydroxy group, a hydroxy-substituted lower alkoxy group and a lower alkanoyloxy group, R^3 is a hydrogen atom and A is a lower alkylene group, or a salt thereof.
- 10 (3) The carbostyryl derivative of the formula (1) wherein R^1 and R^2 are a lower alkyl group having optionally a substituent selected from a hydroxy group, a lower alkoxy group, a phenyl-lower alkoxy group and a lower alkanoyloxy group, R^3 is a lower alkyl group and A is a lower alkylene group, or a salt thereof.
- 15 (4) The carbostyryl derivative of the formula (1) wherein R^1 is a lower alkyl group having optionally a substituent selected from a hydroxy group, a lower alkoxy group, a phenyl-lower alkoxy group and a lower alkanoyloxy group, R^2 is a cycloalkyl group having optionally a substituent selected from a hydroxy group, a hydroxy-substituted lower alkoxy group and a lower alkanoyloxy group, R^3 is a lower alkyl group and A is a lower alkylene group, or a salt thereof.
- 20

- (5) The carbostyryl derivative of the formula (1) wherein R^1 and R^2 are a lower alkyl group having optionally a substituent selected from a hydroxy group, a lower alkoxy group, a phenyl-lower alkoxy group and a lower alkanoyloxy group, R^3 is a lower alkenyl group and A is a lower alkylene group, or a salt thereof.
- (6) The carbostyryl derivative of the formula (1) wherein R^1 is a lower alkyl group having optionally a substituent selected from a hydroxy group, a lower alkoxy group, a phenyl-lower alkoxy group and a lower alkanoyloxy group, R^2 is a cycloalkyl group having optionally a substituent selected from a hydroxy group, a hydroxy-substituted lower alkoxy group and a lower alkanoyloxy group, R^3 is a lower alkenyl group and A is a lower alkylene group, or a salt thereof.
- (7) The carbostyryl derivative of the formula (1) wherein R^1 and R^2 are a cycloalkyl group having optionally a substituent selected from a hydroxy group, a hydroxy-substituted lower alkoxy group and a lower alkanoyloxy group, R^3 is a hydrogen atom and A is a lower alkylene group, or a salt thereof.
- (8) The carbostyryl derivative of the formula (1) wherein R^1 and R^2 are a cycloalkyl group having optionally a substituent selected from a hydroxy group, a hydroxy-substituted lower alkoxy group and a lower alkanoyloxy group, R^3 is a lower alkyl group and A is a lower alkylene group, or a salt thereof.
- (9) The carbostyryl derivative of the formula (1) wherein R^1 and R^2 are a cycloalkyl group having optionally a substituent selected from a hydroxy

group, a hydroxy-substituted lower alkoxy group and a lower alkanoyloxy group, R^3 is a lower alkenyl group and A is a lower alkylene group, or a salt thereof.

(10) The carbostyryl derivative of the formula (1) wherein R^1 and R^2 are a
5 lower alkyl group having optionally a substituent selected from a hydroxy group, a lower alkoxy group, a phenyl-lower alkoxy group and a lower alkanoyloxy group, R^3 is a hydroxy-substituted lower alkyl group and A is a lower alkylene group, or a salt thereof.

(11) The carbostyryl derivative of the formula (1) wherein R^1 is a lower alkyl
10 group having optionally a substituent selected from a hydroxy group, a lower alkoxy group, a phenyl-lower alkoxy group and a lower alkanoyloxy group, R^2 is a cycloalkyl group having optionally a substituent selected from a hydroxy group, a hydroxy-substituted lower alkoxy group and a lower alkanoyloxy group, R^3 is a hydroxy-substituted lower alkyl group and A is a lower alkylene
15 group, or a salt thereof.

(12) The carbostyryl derivative of the formula (1) wherein R^1 and R^2 are a
cycloalkyl group having optionally a substituent selected from a hydroxy group, a hydroxy-substituted lower alkoxy group and a lower alkanoyloxy group, R^3 is a hydroxy-substituted lower alkyl group and A is a lower alkylene
20 group, or a salt thereof.

(13) The carbostyryl derivative of the formula (1) wherein R^1 and R^2 are an amino group having optionally a substituent selected from a lower alkyl group and a cycloalkyl group, R^3 is a hydrogen atom and A is a lower alkylene group,

or a salt thereof.

(14) The carbostyryl derivative of the formula (1) wherein R¹ is an amino group having optionally a substituent selected from a lower alkyl group and a cycloalkyl group, R² is a lower alkyl group having optionally a substituent
5 selected from a hydroxy group, a lower alkoxy group, a phenyl-lower alkoxy group and a lower alkanoyloxy group, R³ is a hydrogen atom and A is a lower alkylene group, or a salt thereof.

(15) The carbostyryl derivative of the formula (1) wherein R¹ is an amino group having optionally a substituent selected from a lower alkyl group and a
10 cycloalkyl group, R² is a cycloalkyl group having optionally a substituent selected from a hydroxy group, a hydroxy-substituted lower alkoxy group and a lower alkanoyloxy group, R³ is a hydrogen atom and A is a lower alkylene group, or a salt thereof.

(16) The carbostyryl derivative of the formula (1) wherein R¹ and R² are an
15 amino group having optionally a substituent selected from a lower alkyl group and a cycloalkyl group, R³ is a lower alkyl group and A is a lower alkylene group, or a salt thereof.

(17) The carbostyryl derivative of the formula (1) wherein R¹ is an amino group having optionally a substituent selected from a lower alkyl group and a
20 cycloalkyl group, R² is a lower alkyl group having optionally a substituent selected from a hydroxy group, a lower alkoxy group, a phenyl-lower alkoxy group and a lower alkanoyloxy group, R³ is a lower alkyl group and A is a

lower alkylene group, or a salt thereof.

(18) The carbostyryl derivative of the formula (1) wherein R^1 is an amino group having optionally a substituent selected from a lower alkyl group and a cycloalkyl group, R^2 is a cycloalkyl group having optionally a substituent
5 selected from a hydroxy group, a hydroxy-substituted lower alkoxy group and a lower alkanoyloxy group, R^3 is a lower alkyl group and A is a lower alkylene group, or a salt thereof.

(19) The carbostyryl derivative of the formula (1) wherein R^1 and R^2 are an amino group having optionally a substituent selected from a lower alkyl group
10 and a cycloalkyl group, R^3 is a lower alkenyl group and A is a lower alkylene group, or a salt thereof.

(20) The carbostyryl derivative of the formula (1) wherein R^1 is an amino group having optionally a substituent selected from a lower alkyl group and a cycloalkyl group, R^2 is a lower alkyl group having optionally a substituent
15 selected from a hydroxy group, a lower alkoxy group, a phenyl-lower alkoxy group and a lower alkanoyloxy group, R^3 is a lower alkenyl group and A is a lower alkylene group, or a salt thereof.

(21) The carbostyryl derivative of the formula (1) wherein R^1 is an amino group having optionally a substituent selected from a lower alkyl group and a
20 cycloalkyl group, R^2 is a cycloalkyl group having optionally a substituent selected from a hydroxy group, a hydroxy-substituted lower alkoxy group and a lower alkanoyloxy group, R^3 is a lower alkenyl group and A is a lower

alkylene group, or a salt thereof.

(22) The carbostyryl derivative of the formula (1) wherein R¹ and R² are an amino group having optionally a substituent selected from a lower alkyl group and a cycloalkyl group, R³ is a hydroxy-substituted lower alkyl group and A is a lower alkylene group, or a salt thereof.

(23) The carbostyryl derivative of the formula (1) wherein R¹ is an amino group having optionally a substituent selected from a lower alkyl group and a cycloalkyl group, R² is a lower alkyl group having optionally a substituent selected from a hydroxy group, a lower alkoxy group, a phenyl-lower alkoxy group and a lower alkanoyloxy group, R³ is a hydroxy-substituted lower alkyl group and A is a lower alkylene group, or a salt thereof.

(24) The carbostyryl derivative of the formula (1) wherein R¹ is an amino group having optionally a substituent selected from a lower alkyl group and a cycloalkyl group, R² is a cycloalkyl group having optionally a substituent selected from a hydroxy group, a hydroxy-substituted lower alkoxy group and a lower alkanoyloxy group, R³ is a hydroxy-substituted lower alkyl group and A is a lower alkylene group, or a salt thereof.

(25) 6-{3-[3-(trans-2-Hydroxycyclohexyl)-3-cyclopropylureido]propoxy}-carbostyryl

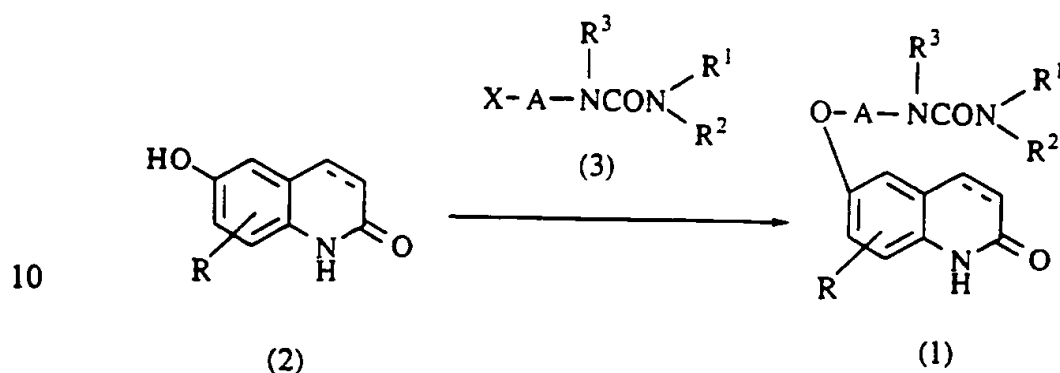
(26) (S,S)-(+)-6-{3-[3-(2-Hydroxycyclohexyl)-3-cyclopropylureido]propoxy}-carbostyryl

(27) (R,R)-(-)-6-{3-[3-(2-Hydroxycyclohexyl)-3-cyclopropylureido]propoxy}-carbostyryl

(28) 6-{3-[3-(2-Hydroxycyclobutyl)-3-cyclopropylureido]propoxy}-carbostyryl

The carbostyryl derivatives of the above formula (1) can be prepared by various processes, for example, by the following processes.

5 Reaction Scheme-1

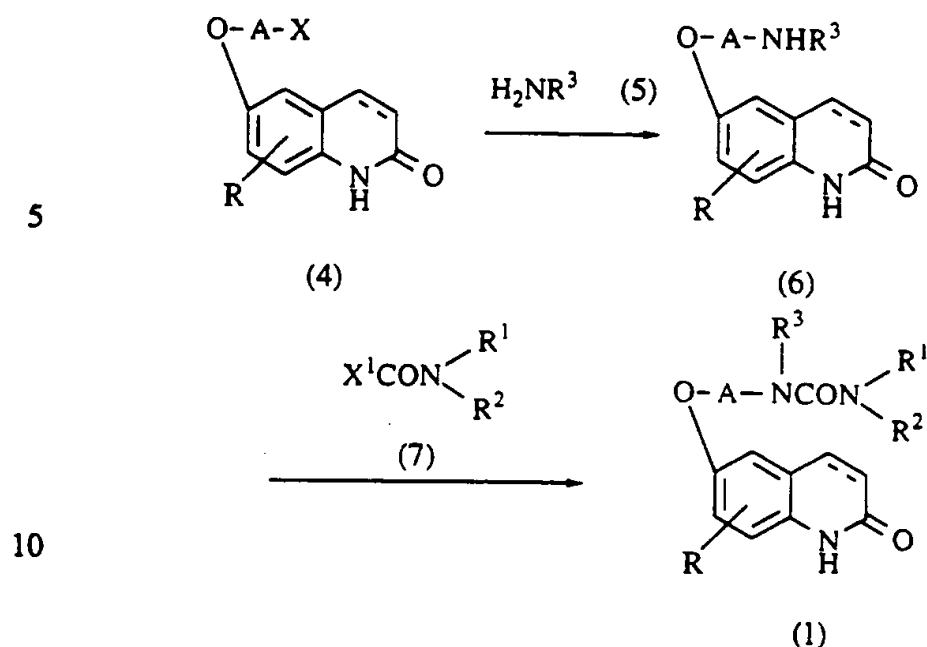


15 wherein R, R¹, R², R³, A and the bond between 3- and 4-positions of the carbostyryl nucleus are the same as defined above, X is a halogen atom, a lower alkanesulfonyloxy group, an arylsulfonyloxy group, or an aralkylsulfonyloxy group.

20 The reaction of the compound (2) and the compound (3) is carried out in a suitable solvent, preferably by using a basic compound as a de-halogen hydride agent at a temperature from room temperature to 200°C, preferably at a temperature from room temperature to 150°C, for about 1 hour to about 75 hours. The suitable solvent includes, for example, lower alcohols (e.g. methanol, ethanol, isopropanol, etc.), ketones (e.g. acetone, methyl ethyl ketone, etc.), ethers (e.g. diethyl ether, dioxane, diethylene glycol dimethyl ether, etc.), aromatic hydrocarbons (e.g. benzene, toluene, xylene, etc.), dimethylformamide, dimethyl sulfoxide, hexamethylphosphoric triamide, etc. The basic compound

used as a de-halogen hydride agent includes, for example, inorganic bases (e.g. sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium methoxide, sodium ethoxide, potassium ethoxide, sodium hydride, metal potassium, sodium amide, etc.), or organic bases (e.g. pyridine, quinoline, triethylamine, tripropylamine, etc.). There may be added an alkali metal iodide such as potassium iodide, sodium iodide, as a reaction promoter. The amount of the compound (3) is not critical, but it is usually in the range of 1 mole to 5 moles, preferably in the range of 1 mole to 3 moles, to 1 mole of the compound (2).

10 In the above Reaction Scheme-1, the halogen atom for X is fluorine atom, chlorine atom, bromine atom or iodine atom. The lower alkanesulfonyloxy group for X includes methanesulfonyloxy, ethanesulfonyloxy, isopropanesulfonyloxy, propanesulfonyloxy, butanesulfonyloxy, t-butanesulfonyloxy, pentanesulfonyloxy, hexanesulfonyloxy, etc. The arylsulfonyloxy group for X
15 includes a substituted or unsubstituted arylsulfonyloxy group such as phenylsulfonyloxy, 4-methylphenylsulfonyloxy, 2-methylphenylsulfonyloxy, 4-nitrophenylsulfonyloxy, 4-methoxyphenylsulfonyloxy, 3-chlorophenylsulfonyloxy, α -naphthylphenylsulfonyloxy, etc. The aralkylsulfonyloxy group for X
20 includes a substituted or unsubstituted aralkylsulfonyloxy group such as benzylsulfonyloxy, 2-phenylethylsulfonyloxy, 4-phenylbutylsulfonyloxy, 4-methylbenzylsulfonyloxy, 2-methylbenzylsulfonyloxy, 4-nitrobenzylsulfonyloxy, 4-methoxybenzylsulfonyloxy, 3-chlorobenzylsulfonyloxy, α -naphthylmethylsulfonyloxy, etc.

Reaction Scheme-2

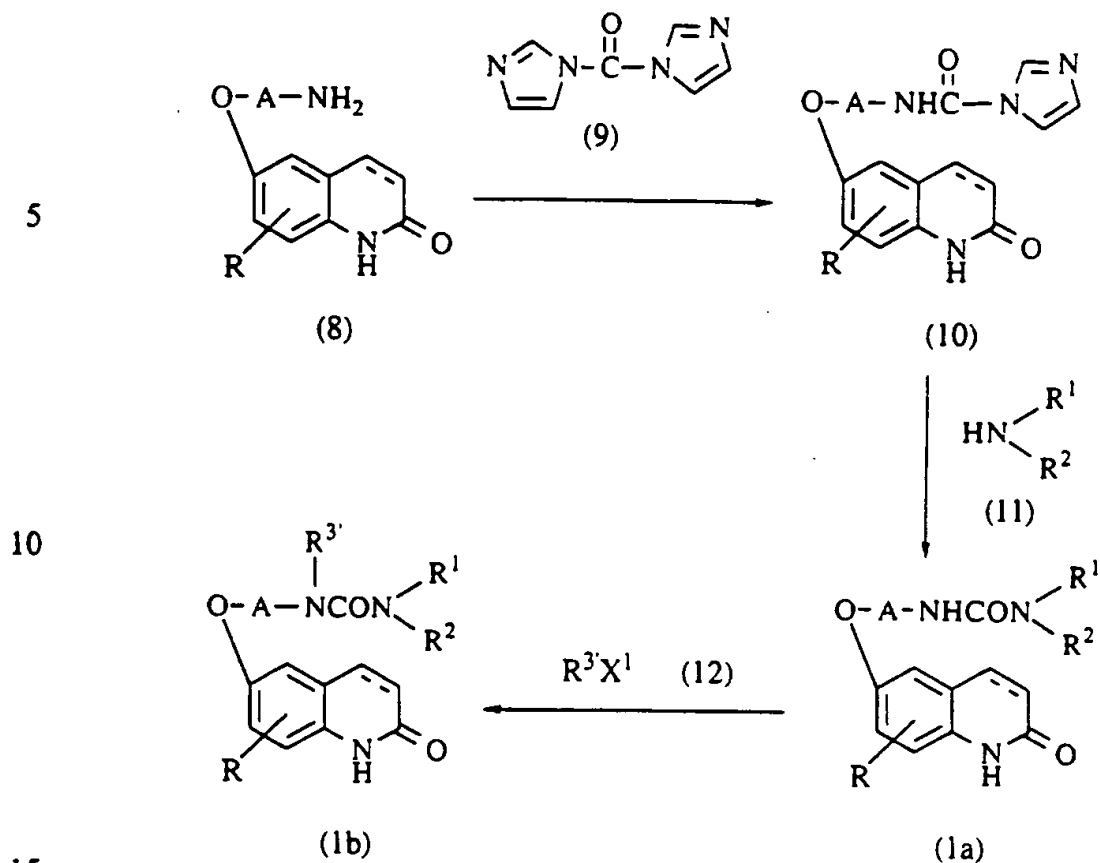
wherein R, R¹, R², R³, A, X and the bond between 3- and 4-positions of the carbostyryl nucleus are the same as defined above, and X¹ is a halogen atom.

15 The reaction of the compound (4) and the compound (5) is carried out in a suitable solvent or without a solvent in the presence or absence of a basic compound. The reaction is usually carried out at a temperature from room temperature to 200°C, preferably at a temperature from room temperature to 150°C, for 1 hour to about 30 hours. The solvent includes, for example, ethers (e.g. dioxane, tetrahydrofuran, ethylene glycol dimethyl ether, diethyl ether, 20 etc.), aromatic hydrocarbons (e.g. benzene, toluene, xylene, etc.), halogenated hydrocarbons (e.g. dichloromethane, chloroform, carbon tetrachloride, etc.), lower alcohols (e.g. methanol, ethanol, isopropanol, etc.), water, polar solvents (e.g. dimethylformamide, dimethyl sulfoxide, hexamethylphosphoric triamide, pyridine, acetone, acetonitrile, etc.), or a mixture thereof. The basic compound

includes, for example, inorganic bases (e.g. potassium carbonate, sodium carbonate, sodium hydroxide, potassium hydroxide, sodium hydrogen carbonate, potassium hydrogen carbonate, sodium amide, sodium hydride, potassium hydride, etc.), organic bases (e.g. triethylamine, tripropylamine, pyridine, quinoline, etc.), etc. There may be added an alkali metal iodide (e.g. potassium iodide, sodium iodide, etc.) as a reaction promoter. The compound (5) may usually be used at least in an equimolar amount, preferably in an excess amount, to 1 mole of the compound (4). When the compound (5) is vaporous, the reaction may be carried out in a sealed tube.

10 In the above Reaction Scheme-2, the halogen atom for X^1 is fluorine atom, chlorine atom, bromine atom or iodine atom.

The reaction of the compound (6) and the compound (7) is carried out under the same conditions as those in the reaction of the compound (2) and the compound (3) in the above Reaction Scheme-1.

Reaction Scheme-3

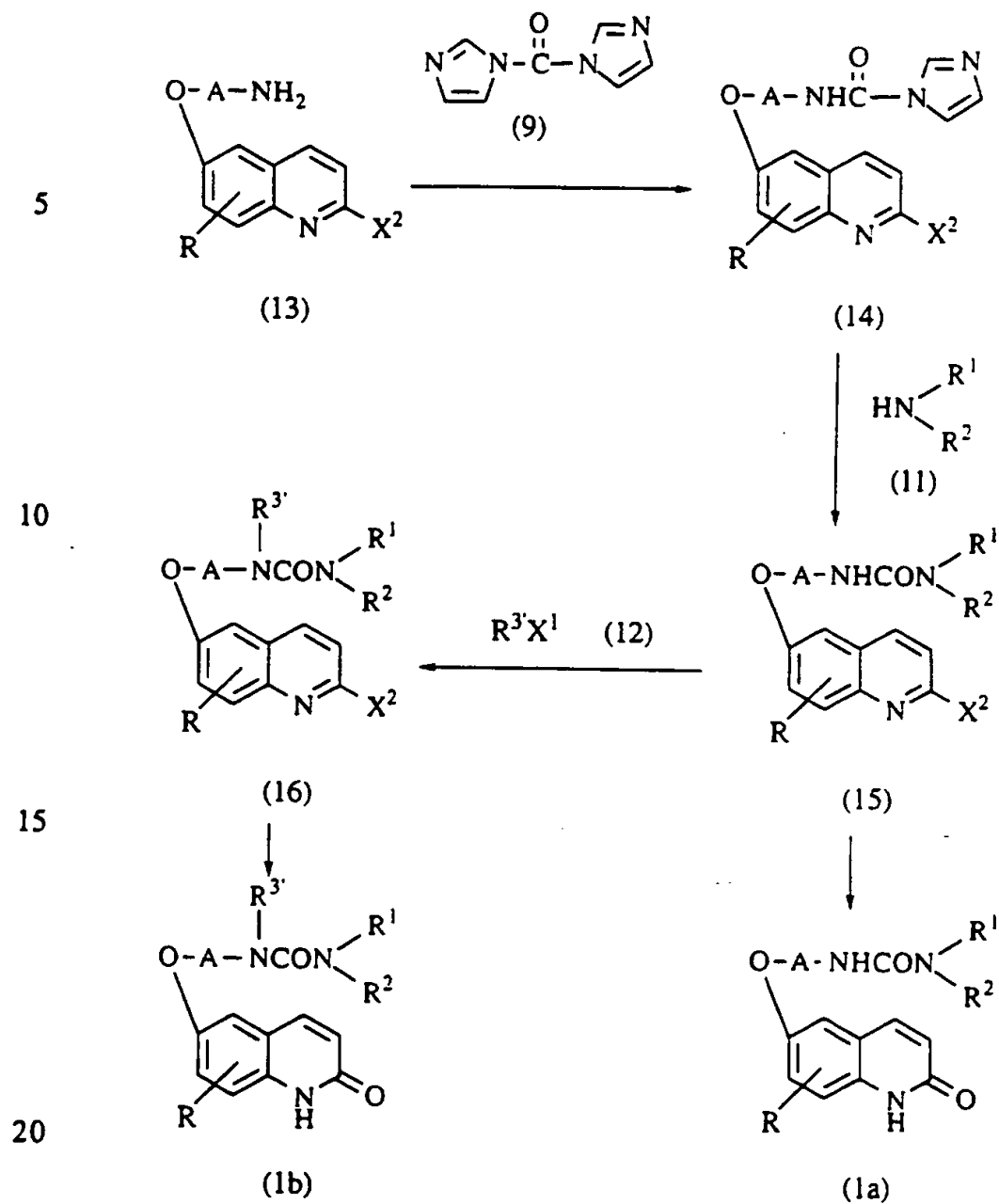
wherein R , R^1 , R^2 , A , X^1 and the bond between 3- and 4-positions of the carbostyryl nucleus are the same as defined above, and R^3 is a lower alkyl group, a lower alkenyl group or a hydroxy-substituted lower alkyl group.

The reaction of the compound (8) and the compound (9) is carried out in the presence of imidazole in a suitable solvent. The solvent may be the same solvents for the reaction of the compound (4) and the compound (5) in the above Reaction Scheme-2. The compound (9) is usually used at least in an equimolar amount, preferably in an amount of 1 mole to 1.5 mole, to 1 mole of the compound (8). Imidazole is usually used at least in an equimolar amount,

preferably in an amount of 1 mole to 4 moles, to 1 mole of the compound (8). The reaction is usually carried out at a temperature from -20°C to 150°C , preferably at a temperature from -20°C to about 100°C , for 1 hour to about 30 hours.

- 5 The reaction of the compound (10) and the compound (11) is carried out in a suitable solvent. The solvent may be the same solvents for the reaction of the compound (4) and the compound (5) in the above Reaction Scheme-2. The compound (11) is usually used at least in an equimolar amount, preferably in an amount of 1 mole to 1.5 mole, to 1 mole of the compound (10). The reaction is
10 usually carried out at a temperature from room temperature to 150°C , preferably at a temperature from room temperature to about 100°C , for 1 hour to about 15 hours.

- The reaction of the compound (1a) and the compound (12) is carried out under the same condition as those in the reaction of the compound (2) and the
15 compound (3) in the above Reaction Scheme-1 except that the compound (12) is used at least in an equimolar, preferably in an amount of 1 mole to 5 moles, to 1 mole of the compound (1a).

Reaction Scheme-4

wherein R, R¹, R², R^{3'}, A and X are the same as defined above, and X² is a halogen atom.

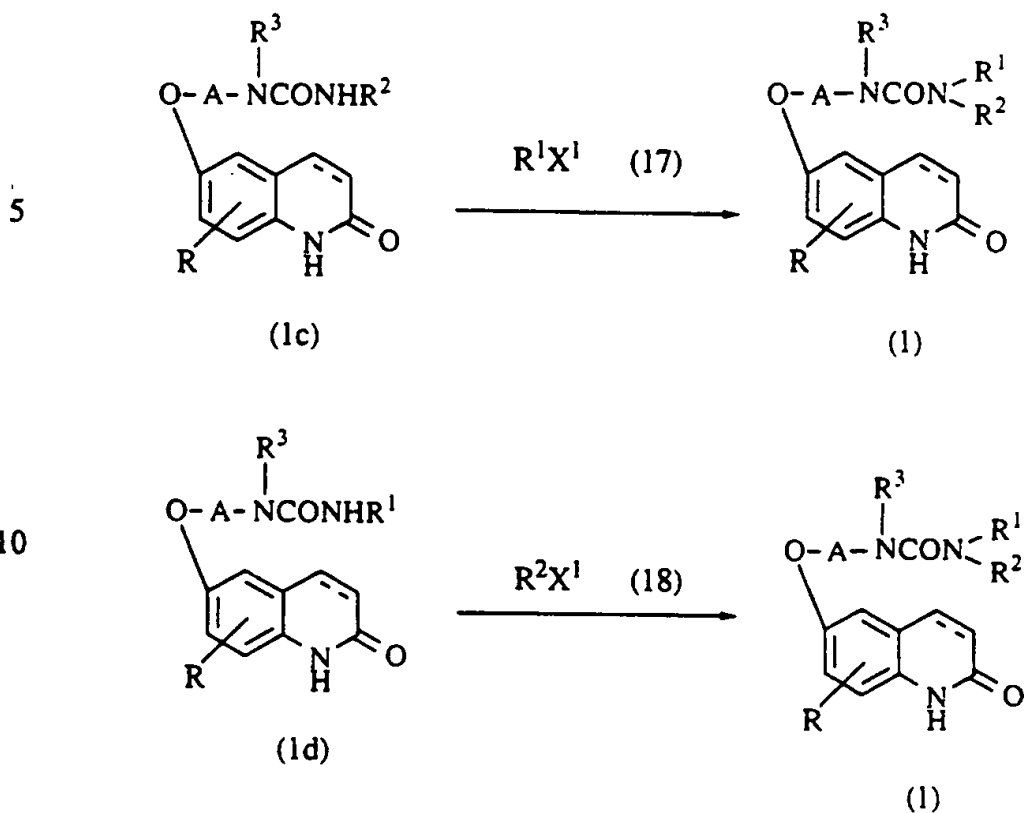
The reaction of the compound (13) and the compound (9) is carried out

under the same conditions as those in the reaction of the compound (8) and the compound (9) in the above Reaction Scheme-3.

The reaction of the compound (14) and the compound (11) is carried out under the same conditions as those in the reaction of the compound (10) and the compound (11) in the above Reaction Scheme-3.

The reaction of the compound (15) and the compound (12) is carried out under the same conditions as those in the reaction of the compound (1a) and the compound (12) in the above Reaction Scheme-3.

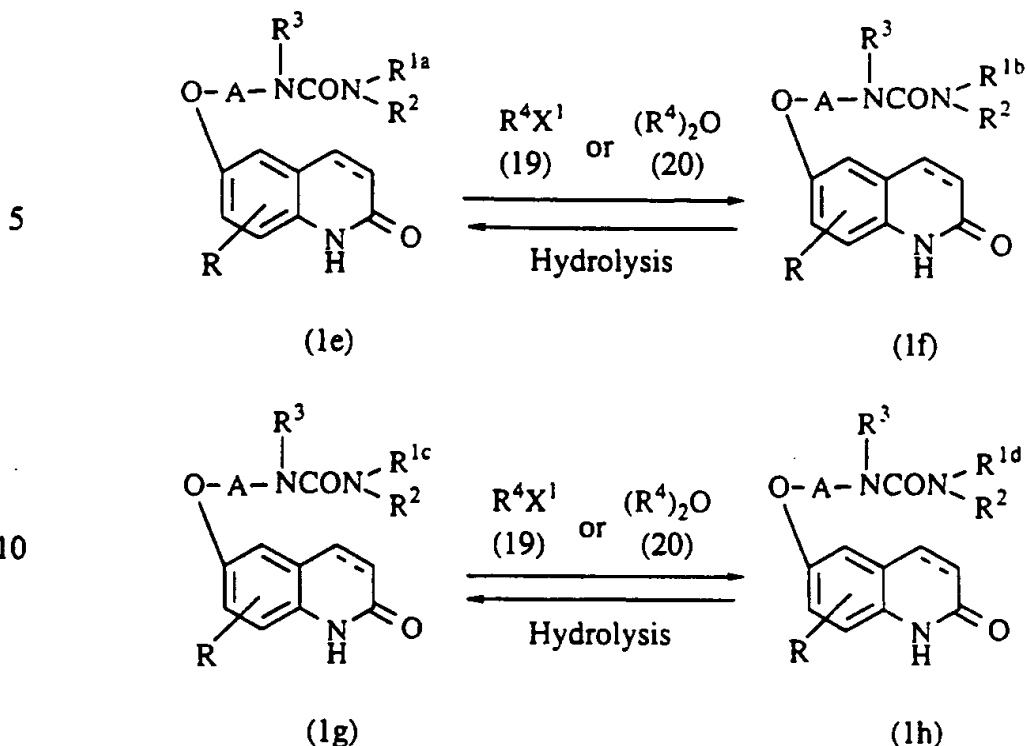
The reaction of converting the compound (16) into the compound (1b), and the reaction of converting the compound (15) into the compound (1a) are carried out by heating the compound (16) or the compound (15) in the presence of a hydrohalogenic acid such as hydrochloric acid, hydrobromic acid, etc., an inorganic acid such as sulfuric acid, phosphoric acid, etc., an alkali metal hydroxide such as potassium hydroxide, potassium hydroxide, etc., an inorganic alkali metal compound such as sodium carbonate, potassium carbonate, potassium hydrogen carbonate, etc., or an organic acid such as acetic acid, at a temperature from 50°C to 150°C, preferably at a temperature from 70°C to 120°C, for 0.5 hour to about 24 hours.

Reaction Scheme-5

15 wherein R , R^1 , R^2 , R^3 , A , X^1 and the bond between 3- and 4-positions of the carboxtyril nucleus are the same as defined above.

The reaction of the compound (1c) and the compound (17), and the reaction of the compound (1d) and the compound (18) are carried out under the same conditions as those in the reaction of the compound (1a) and the compound (12) in the above Reaction Scheme-3.

20

Reaction Scheme-6

wherein R, R², R³, A, X¹ and the bond between 3- and 4-positions of the carbostyryl nucleus are the same as defined above, R^{1a} is a lower alkyl group having a hydroxy substituent, R^{1b} is a lower alkyl group having a lower alkanoyloxy substituent, R^{1c} is a cycloalkyl group having a hydroxy substituent, R^{1d} is a cycloalkyl group having a lower alkanoyloxy substituent, and R⁴ is a lower alkanoyl group.

The reaction of the compound (1e) and the compound (19), and the reaction of the compound (1g) and the compound (19) are carried out in a suitable inert solvent in the presence or absence of a basic compound. The inert solvent includes, for example, aromatic hydrocarbons (e.g. benzene, toluene,

xylene, etc.), ethers (e.g. tetrahydrofuran, dioxane, diethylene glycol dimethyl ether, etc.), halogenated hydrocarbons (e.g. dichloromethane, chloroform, carbon tetrachloride, etc.), lower alcohols (e.g. methanol, ethanol, isopropanol, butanol, t-butanol, etc.), acetic acid, ethyl acetate, acetone, acetonitrile, pyridine, 5 dimethyl sulfoxide, dimethylformamide, hexamethylphosphoric triamide, or a mixture thereof. The basic compound includes, for example, carbonates or hydrogen carbonates (e.g. sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogen carbonate, etc.), alkali metal hydroxides (e.g. sodium hydroxide, potassium hydroxide, etc.), sodium hydride, 10 sodium, potassium, sodium amide, alkali metal alkylates (e.g. sodium methylate, sodium ethylate, etc.), organic bases such as pyridine, N-ethyldiisopropylamine, dimethylaminopyridine, triethylamine, 1,5-diazabicyclo[4.3.0]nonen-5 (DBU), 1,8-biazabicyclo[5.4.0]undecen-7 (DBU), 1,4-diazabicyclo[2.2.2]octane (DABCO), etc. The ratio of the compound (1e) and the compound (19), and the 15 ratio of the compound (1g) and the compound (19) are not critical, but the latter is usually used at least in an equimolar amount, preferably in an amount of 1 mole to 10 moles, to 1 mole of the former compound, respectively. The reaction is usually carried out at a temperature from 0°C to about 200°C, preferably at a temperature from 0°C to about 100°C, for 30 minutes to about 75 hours. There 20 may be added an alkali metal halide such as sodium iodide, potassium iodide, etc., or a copper powder, as a reaction promoter.

The reaction of the compound (1e) and the compound (20), and the reaction of the compound (1g) and the compound (20) are carried out in a suitable solvent or without a solvent in the presence or absence of a basic

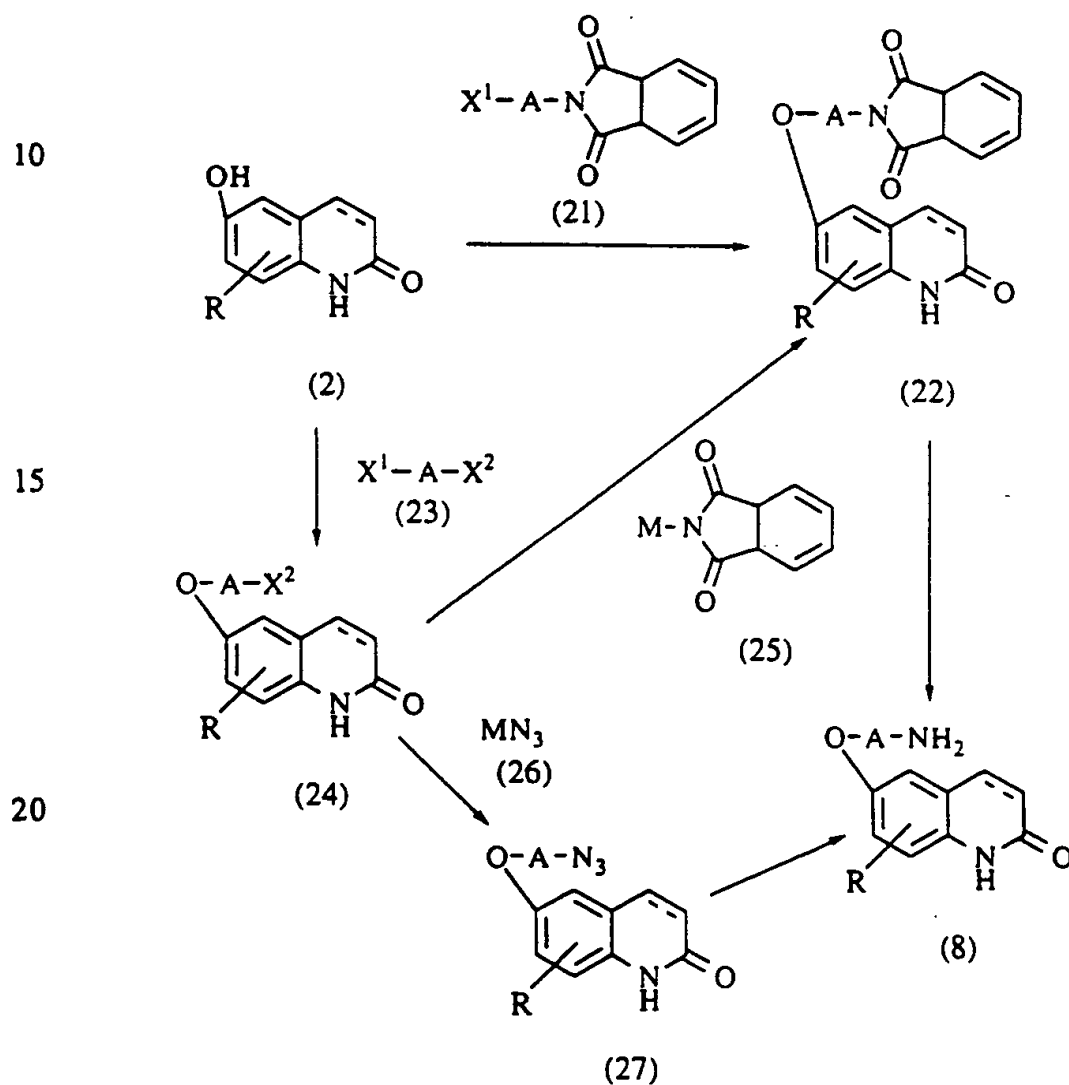
compound, preferably in the presence of a basic compound. The solvent includes, for example, the above mentioned aromatic hydrocarbons, lower alcohols (e.g. methanol, ethanol, propanol, etc.), dimethylformamide, dimethyl sulfoxide, halogenated hydrocarbons (e.g. chloroform, methylene chloride, etc.), acetone, pyridine, etc. The basic compound includes, for example, organic bases such as triethylamine, pyridine, 4-dimethylaminopyridine, etc., sodium hydroxide, potassium hydroxide, sodium hydride, or a mixture thereof. The above reaction can be also carried out in a solvent such as acetic acid, in the presence of a mineral acid such as sulfuric acid. The compound (20) is used in an amount of 1 mole to excess amount, to 1 mole of the starting compound (1e) or (1g). The reaction is usually carried out at a temperature from 0°C to about 200°C, preferably at a temperature from 0°C to about 150°C, for 0.5 hour to about 20 hours.

The hydrolysis of the compound (1f) or the compound (1h) is carried out in a suitable solvent or without a solvent in the presence of an acid or a basic compound. The solvent includes, for example, water, lower alcohols (e.g. methanol, ethanol, isopropanol, etc.), ketones (e.g. acetone, methyl ethyl ketone, etc.), ethers (e.g. dioxane, tetrahydrofuran, ethylene glycol dimethyl ether, etc.), fatty acids (e.g. acetic acid, formic acid, etc.), or a mixture thereof. The acid includes, for example, mineral acids (e.g. hydrochloric acid, sulfuric acid, hydrobromic acid, etc.), organic acids (e.g. formic acid, acetic acid, aromatic sulfonic acid, etc.), etc. The basic compound includes, for example, an alkali metal carbonate (e.g. sodium carbonate, potassium carbonate, etc.), a metal hydroxide (e.g. sodium hydroxide, potassium hydroxide, calcium hydroxide, lithium

hydroxide, etc.), etc. The reaction is usually carried out at a temperature from room temperature to about 200°C, preferably at a temperature from room temperature to about 150°C, for 10 minutes to about 25 hours.

The starting compounds of the formulae (3), (7), (8), (11) and (13) used in the above Reaction Schemes-1, -2, -3, and -4 are prepared by the following processes.

Reaction Scheme-7



wherein R, A, X¹, X² and the bond between 3- and 4-positions of the carbostyryl nucleus are the same as defined above, and M is an alkali metal atom such as sodium, potassium, etc.

The reaction of the compound (2) and the compound (21), and the
5 reaction of the compound (2) and the compound (23) are carried out under the same conditions as those in the reaction of the compound (2) and the compound (3) in the above Reaction Scheme-1.

The reaction of the compound (24) and the compound (25) is carried out in a suitable solvent at a temperature from room temperature to 200°C,
10 preferably at a temperature from room temperature to 150°C, for 1 hour to about 15 hours. The solvent may be the same solvents for the reaction of the compound (2) and the compound (3) in the above Reaction Scheme-1. The compound (25) is usually used at least in an equimolar amount, preferably in an amount of 1 mole to 2 moles, to 1 mole of the compound (24). There may be
15 added an alkali metal iodide such as sodium iodide, potassium iodide, or a copper powder, as a reaction promoter.

The reaction of the compound (24) and the compound (26) is carried out under the same conditions as those in the reaction of the compound (24) and the compound (25) as mentioned above.

20 The reaction of converting the compound (22) into the compound (8) is carried out by reacting the compound (22) with hydrazine in a suitable solvent, or by subjecting the compound (22) to hydrolysis.

The solvent used in the reaction of the compound (22) and hydrazine includes, for example, aromatic hydrocarbons (e.g. benzene, toluene, xylene,

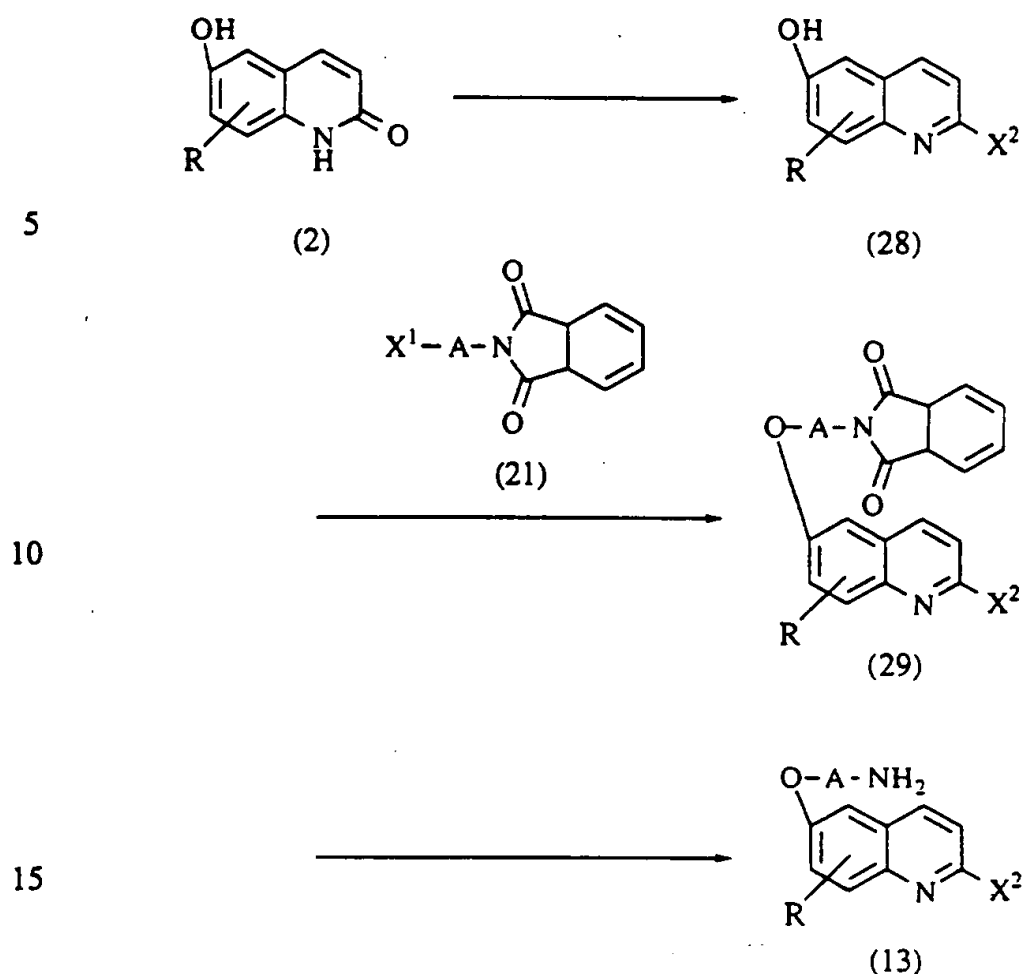
etc.), ethers (e.g. diethyl ether, dioxane, tetrahydrofuran, diethylene glycol dimethyl ether, etc.), alcohols (e.g. methanol, ethanol, isopropanol, butanol, etc.), water, acetic acid, ethyl acetate, acetone, acetonitrile, dimethyl sulfoxide, dimethylformamide, hexamethylphosphoric triamide, etc. Hydrazine is usually
5 used at least in an equimolar amount, preferably in an amount of 1 mole to 5 moles, to 1 mole of the compound (22). The reaction is usually carried out at a temperature from room temperature to 120°C, preferably at a temperature from 0°C to about 100°C, for 0.5 hour to 15 hours.

The hydrolysis of the compound (22) is carried out under the same
10 conditions as those in the hydrolysis of the compound (1f) in the above Reaction Scheme-6.

The reaction of converting the compound (27) into the compound (8) is carried out by subjecting the compound (27) to reduction with using a catalyst in a suitable solvent. The solvent includes, for example, water, acetic acid,
15 alcohols (e.g. methanol, ethanol, isopropanol, etc.), hydrocarbons (e.g. hexane, cyclohexane, etc.), ethers (e.g. diethylene glycol dimethyl ether, dioxane, tetrahydrofuran, diethyl ether, etc.), esters (e.g. ethyl acetate, methyl acetate, etc.), aprotic polar solvents (e.g. N,N-dimethylformamide, etc.), or a mixture thereof. The catalyst includes, for example, palladium, palladium-black,
20 palladium-carbon, platinum, platinum oxide, copper chromite, Raney-nickel, etc. The catalyst is used in an amount of 0.02-1 time by weight as much as the amount of the compound (27). The reaction is usually carried out at a temperature from -20°C to about 100°C, preferably at a temperature from 0°C to about 80°C, under 1 atm to 10 atms of hydrogen gas, for 0.5 hour to about

20 hours.

The reaction of converting the compound (27) into the compound (8) is also carried out by subjecting the compound (27) to reduction with using a hydrogenation reducing agent. The hydrogenation reducing agent includes, for example, lithium aluminum hydride, lithium borohydride, sodium borohydride, diborane, etc. The hydrogenation reducing agent is used at least in an equimolar amount, preferably in an amount of 1 mole to 10 moles, to 1 mole of the compound (27). The reduction reaction is usually carried out in a suitable solvent such as water, lower alcohols (e.g. methanol, ethanol, isopropanol, etc.), ethers (e.g. tetrahydrofuran, diethyl ether, diisopropyl ether, diglyme, etc.), or a mixture thereof, at a temperature from -60°C to 150°C , preferably at a temperature from -30°C to room temperature, for about 10 minutes to about 5 hours. In case that lithium aluminum hydride or diborane is used as a reducing agent, it is preferable to use an anhydrous solvent such as tetrahydrofuran, diethyl ether, diisopropyl ether, diglyme, etc.

Reaction Scheme-8

wherein R, A, X^1 and X^2 are the same as defined above.

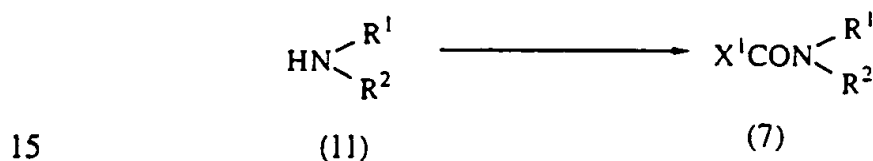
The reaction of converting the compound (2) into the compound (28) is carried out by reacting the compound (2) with a halogenating agent in a suitable inert solvent or without a solvent. The halogenating agent includes, for example, N,N-diethyl-1,2,2-trichlorovinylamide, phosphorus pentachloride, phosphorus pentabromide, phosphorus oxychloride, thionyl chloride, etc. The inert solvent includes, for example, ethers (e.g. dioxane, tetrahydrofuran, etc.), halogenated hydrocarbons (e.g. dichloromethane, dichloroethane, chloroform,

carbon tetrachloride, etc.), etc. The halogenating agent is usually used at least in an equimolar amount, preferably in an excess amount, to 1 mole of the compound (2). The reaction is usually carried out at a temperature from room temperature to 150°C, preferably at a temperature from room temperature to about 120°C, for about 1 hour to about 6 hours.

The reaction of the compound (28) and the compound (21) is carried out under the same conditions as those in the reaction of the compound (2) and the compound (3) in the above Reaction Scheme-1.

The reaction of converting the compound (29) into the compound (13) is carried out under the same conditions as those in the reaction of converting the compound (22) into the compound (8) in the above Reaction Scheme-7.

Reaction Scheme-9

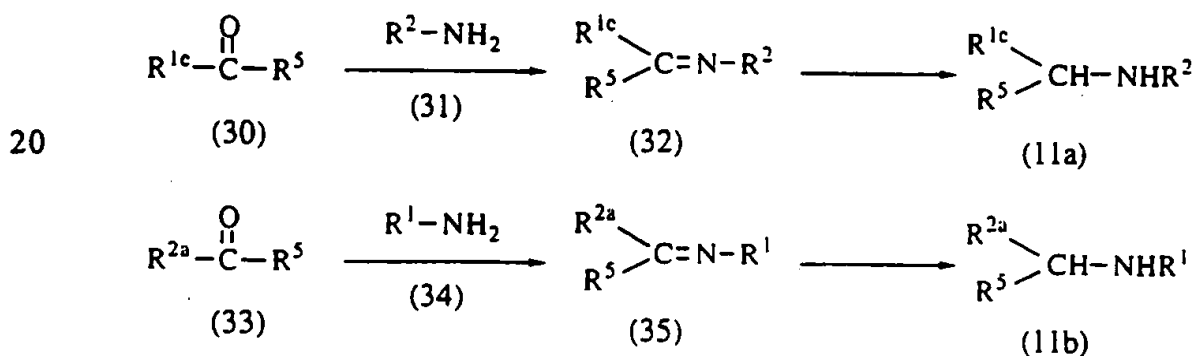


wherein R¹, R² and X¹ are the same as defined above.

The reaction of converting the compound (11) into the compound (7) is carried out by reacting the compound (11) with a carbonylating agent in the presence of a basic compound in a suitable solvent. The solvent includes, for example, halogenated hydrocarbons (e.g. dichloromethane, dichloroethane, chloroform, carbon tetrachloride, etc.), aromatic hydrocarbons (e.g. benzene, p-chlorobenzene, toluene, xylene, etc.), ethers (e.g. diethyl ether, diisopropyl ether, tetrahydrofuran, dimethoxyethane, etc.), esters (e.g. methyl acetate, ethyl acetate, etc.), alcohols (e.g. methanol, ethanol, propanol, butanol, 3-methoxy-1-

butanol, ethyl cellosolve, methyl cellosolve, etc.), water, acetone, acetonitrile, pyridine, dimethyl sulfoxide, dimethylformamide, hexamethylphosphoric triamide, or a mixture thereof. The basic compound includes, for example, inorganic bases such as alkali metal carbonates or hydrogen carbonates (e.g. sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogen carbonate, etc.), alkali metal hydroxides (e.g. sodium hydroxide, potassium hydroxide, etc.), sodium hydride, potassium hydride, etc., organic bases such as pyridine, trimethylamine, triethylamine, dimethylaniline, 1-methyl-2-pyrrolidinone (NMP), N-methylmorpholine, 1,5-diazabicyclo[4.3.0]nonen-5 (DBU), 1,8-biazabicyclo[5.4.0]undecen-7 (DBU), 1,4-diazabicyclo[2.2.2]octane (DABCO), etc. The carbonylating agent includes, for example, phosgene, diphosgene, triphosgene, etc. The carbonylating agent is usually used in an amount of 0.05 mole to 10 moles, preferably in an amount of 0.1 mole to 1 mole, to 1 mole of the compound (11). The reaction is usually carried out at a temperature from room temperature to 200°C, preferably at a temperature from room temperature to about 150°C, for 1 hour to about 10 hours.

Reaction Scheme-10



wherein R¹ and R² are the same as defined above, R^{1c} and R^{2a} are each a lower

alkyl group having optionally a substituent selected from a hydroxy group, a lower alkoxy group, a phenyl-lower alkoxy group and a lower alkanoyloxy group, R^5 is a hydrogen atom, or R^{1e} and R^5 , or R^{2a} and R^5 may combine together with $-CO-$ to which they bond to form a cycloalkyl group having optionally a substituent selected from a hydroxy group, a hydroxy-substituted lower alkoxy group and a lower alkanoyloxy group.

The reaction of the compound (30) and the compound (31), and the reaction of the compound (33) and the compound (34) are carried out in the presence or absence of a dehydrating agent in a suitable solvent or without a solvent. The solvent includes, for example, alcohols (e.g. methanol, ethanol, isopropanol, etc.), aromatic hydrocarbons (e.g. benzene, toluene, xylene, etc.), aprotic polar solvents (e.g. dimethylformamide, dimethylacetamide, N-methylpyrrolidone, etc.), etc. The dehydrating agent includes, for example, a conventional drying agent used for the dehydration of a solvent such as molecular sieves, mineral acids (e.g. hydrochloric acid, sulfuric acid, boron trifluoride, etc.), organic acids (e.g. p-toluenesulfonic acid, etc.), etc. The reaction is usually carried out at a temperature from room temperature to about 200°C, preferably at a temperature from room temperature to about 150°C, for 1 hour to about 48 hours. The amount of the compound (31) or the compound (34) is not critical, but they are usually used at least in an equimolar amount, preferably in an amount of 1 mole to 15 moles, to 1 mole of the compound (30) or the compound (33), respectively. The dehydrating agent is used in an excess amount in the case of a drying agent. In the case of an acid, it is used in a catalytic amount. The compound (32) or the compound (35) thus obtained is

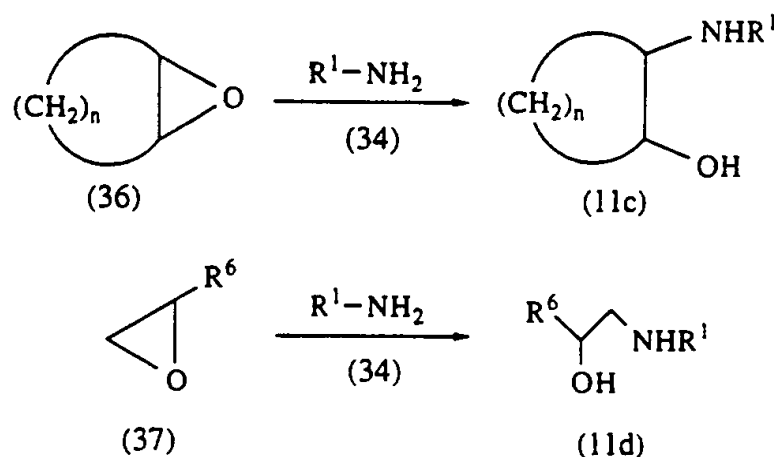
used in the subsequent reduction reaction without isolation.

The reduction of the compound (32) or the compound (35) gives the compound (11a) or the compound (1b), respectively. The reduction reaction may be carried out by a conventional method, for example, by the reduction with using a hydrogenation reducing agent. The hydrogenation reducing agent includes, for example, lithium aluminum hydride, sodium borohydride, diborane, etc. The reducing agent is usually used at least in an equimolar amount, preferably in an amount of 1 mole to 10 moles, to 1 mole of the compound (32) or the compound (35). The reduction is usually carried out in a suitable solvent such as water, lower alcohols (e.g. methanol, ethanol, isopropanol, etc.), ethers (e.g. tetrahydrofuran, diethyl ether, diglyme, etc.), etc. at a temperature from -60°C to about 50°C , preferably at a temperature from -30°C to room temperature, for 10 minutes to about 5 hours. In the case that lithium aluminum hydride or diborane is used as a reducing agent, it is preferable to use an anhydrous solvent such as diethyl ether, tetrahydrofuran, diglyme, etc.

The reduction of the compound (32) or the compound (35) may also be carried out by catalytic hydrogenation in the presence of a catalyst in a suitable solvent. The solvent includes, for example, water, acetic acid, alcohols (e.g. methanol, ethanol, isopropanol, etc.), hydrocarbons (e.g. hexane, cyclohexane, etc.), ethers (e.g. dioxane, tetrahydrofuran, diethyl ether, ethylene glycol dimethyl ether, etc.), esters (e.g. ethyl acetate, methyl acetate, etc.), aprotic polar solvents (e.g. dimethylformamide, etc.), etc. The catalyst includes, for example, palladium, palladium-black, palladium-carbon, platinum, platinum oxide, copper chromite, Raney-nickel, etc. The catalyst is usually used in an amount of 0.02-1

time by weight as much as the amount of the compound (32) or the compound (35). The reaction is usually carried out at a temperature from -20°C to about 150°C , preferably at a temperature from 0°C to about 100°C , under 1 atm to 10 atms of hydrogen gas for 0.5 hour to about 10 hours.

5 Reaction Scheme-11



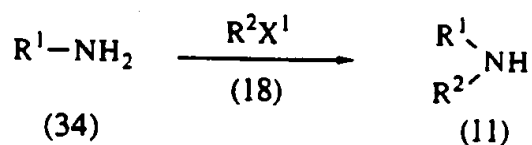
10

wherein R^1 is the same as defined above, n is an integer of 1 to 6, and R^6 is a lower alkyl group.

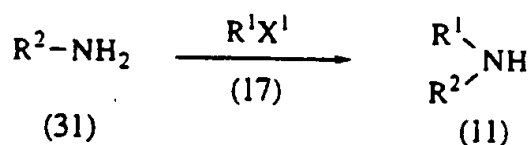
15

The reaction of the compound (36) and the compound (34), and the reaction of the compound (37) and the compound (34) are carried out in a suitable solvent. The solvent may be the same solvents for the reaction of the compound (2) and the compound (3) in the above Reaction Scheme-1. The compound (34) is usually used at least in an equimolar amount, preferably in an amount of 1 mole to 1.5 mole, to 1 mole of the compound (36) or the compound (37). The reaction is usually carried out at a temperature from room temperature to 150°C , preferably at a temperature from room temperature to about 100°C , for 1 hour to about 10 hours.

20

Reaction Scheme-12

5

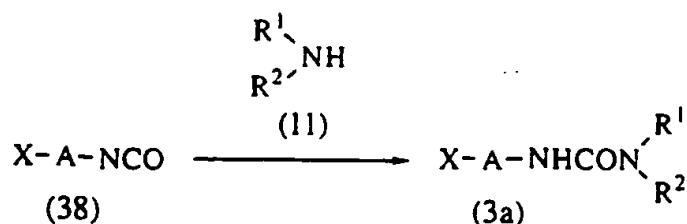


wherein R^1 , R^2 and X^1 are the same as defined above.

10 The reaction of the compound (34) and the compound (18), and the reaction of the compound (31) and the compound (17) are carried out under the same conditions as those in the reaction of the compound (4) and the compound (5) in the above Reaction Scheme-2.

Reaction Scheme-13

15

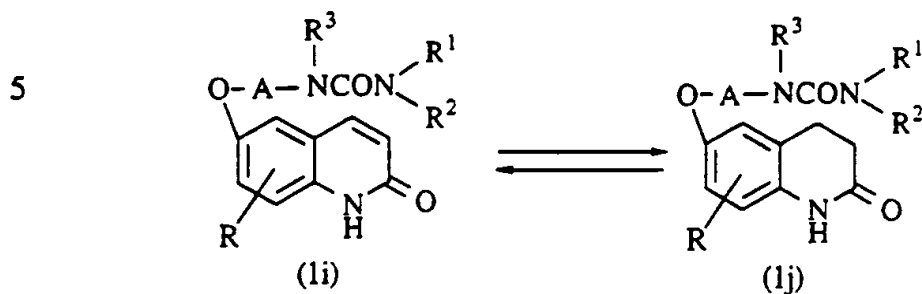


wherein R^1 , R^2 , X and A are the same as defined above.

20 The reaction of the compound (38) and the compound (11) is carried out in the same solvent as in the reaction of the compound (4) and the compound (5) in the above Reaction Scheme-2, at a temperature from room temperature to 100°C, preferably at a temperature from room temperature to about 70°C, for 0.5 hour to about 5 hours. The compound (11) is usually used at least in an

amount of 1 mole to 2 moles, preferably in an amount of 1 mole to 1.5 mole, to 1 mole of the compound (38).

Reaction Scheme-14



wherein R, R¹, R², R³ and A are the same as defined above.

- 10 The reduction of the compound (1i) to convert into the compound (1j) is carried out under conventional catalytic reduction conditions. The catalyst includes, for example, metals such as palladium, palladium-carbon, platinum, Raney-nickel, etc. The catalyst is used in a conventional catalytic amount. The solvent includes, for example, alcohols (e.g. methanol, ethanol, isopropanol, etc.),
- 15 ethers (e.g. dioxane, tetrahydrofuran, etc.), aliphatic hydrocarbons (e.g. hexane, cyclohexane, etc.), esters (e.g. ethyl acetate, etc.), fatty acids (e.g. acetic acid, etc.), etc. The reduction is carried out either under atmospheric pressure, or under pressure, for example, under a pressure from atmospheric pressure to about 20 kg/cm², preferably under a pressure from atmospheric pressure to 10
- 20 kg/cm², at a temperature from 0°C to 150°C, preferably at a temperature from room temperature to about 100°C.

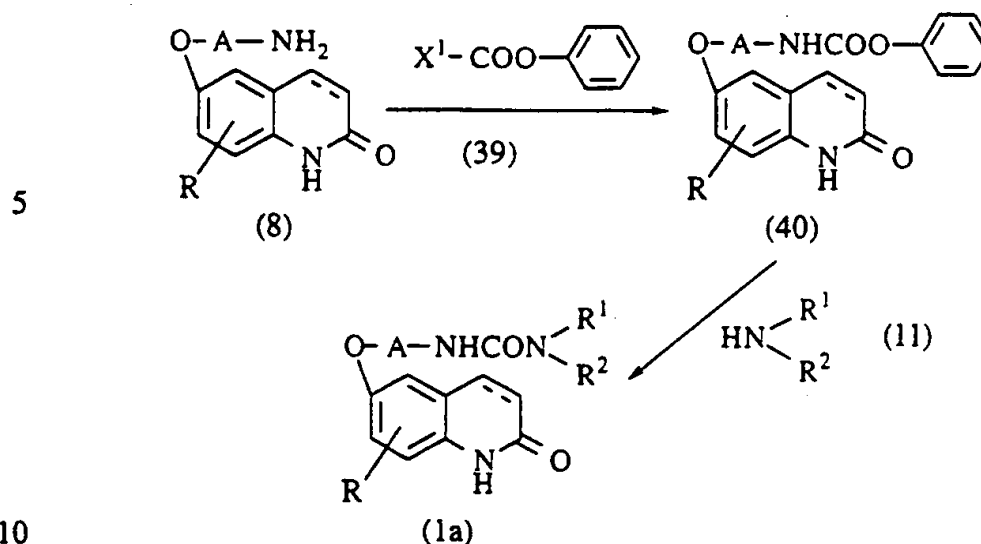
The de-hydrogenation reaction of the compound (1j) to convert into the compound (1i) is carried out by using an oxidizing agent in a suitable solvent. The oxidizing agent includes, for example, benzoquinones (e.g. 2,3-dichloro-

5,6-dicyanobenzoquinone, chloranil (2,3,4,5-tetrachlorobenzoquinone), etc.), halogenating agents (e.g. N-bromosuccinimide, N-chlorosuccinimide, bromine, etc.), catalysts (e.g. selenium dioxide, palladium-carbon, palladium-black, palladium oxide, Raney-nickel, etc.), and the like. The amounts of the benzo-

5 quinones and the halogenating agent are not critical, but it is usually in the range of 1 mole to 15 moles, preferably in the range of 1 mole to 10 moles, to 1 mole of the compound (1j). In case of using a catalyst, it is used in a conventional catalytic amount. The solvent includes, for example, ethers (e.g. dioxane, tetrahydrofuran, methoxyethanol, dimethoxyethane, etc.), aromatic

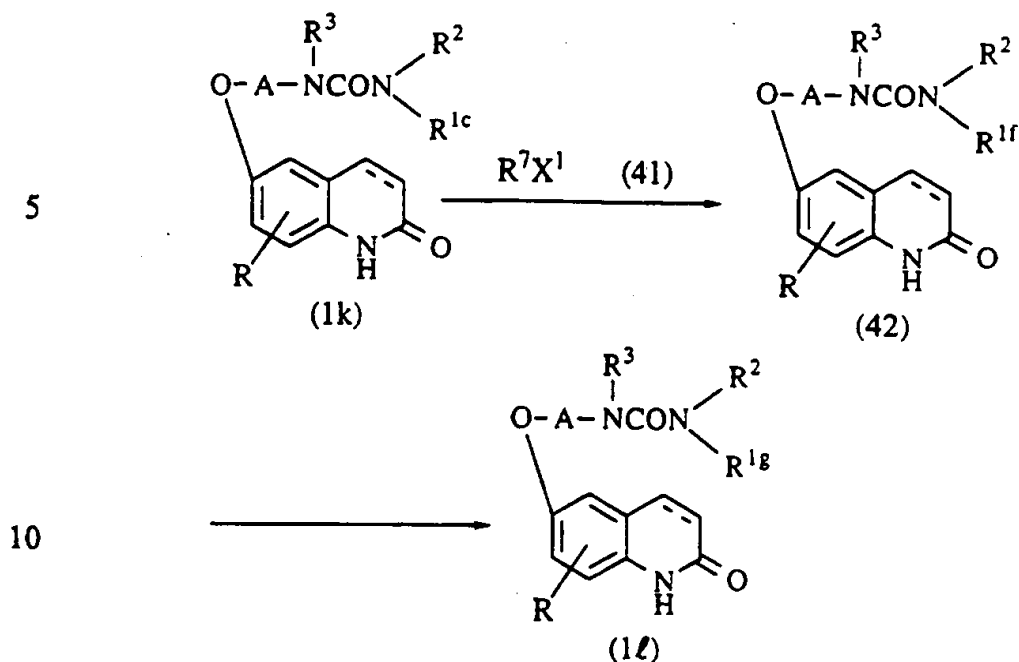
10 hydrocarbons (e.g. benzene, toluene, xylene, cumene, etc.), halogenated hydrocarbons (e.g. dichloromethane, dichloroethane, chloroform, carbon tetrachloride, etc.), alcohols (e.g. butanol, amyl alcohol, hexanol, etc.), polar protic solvents (e.g. acetic acid, etc.), polar aprotic solvents (e.g. dimethylformamide, dimethyl sulfoxide, hexamethylphosphoric triamide, etc.),

15 etc. The reaction is usually carried out at a temperature from room temperature to about 300°C, preferably at a temperature from room temperature to about 200°C, for 1 hour to 40 hours.

Reaction Scheme-15

wherein R, R¹, R², X¹ and A are the same as defined above.

The reaction of the compound (8) and the compound (39) is carried out in the presence of a basic compound in a suitable solvent. The solvent and the basic compound are the same ones as those in the reaction of the compound (4) and the compound (5) in the above Reaction Scheme-2. The reaction is usually carried out at a temperature from -20°C to 50°C, preferably at a temperature from -20°C to room temperature, for 30 minutes to about 5 hours. The compound (39) is used at least in an equimolar amount, preferably in an amount of 1 mole to 2 moles, to 1 mole of the compound (8). The reaction of the compound (40) and the compound (11) is carried out under the same conditions as those in the reaction of the compound (10) and the compound (11) in the above Reaction Scheme-3.

Reaction Scheme-16

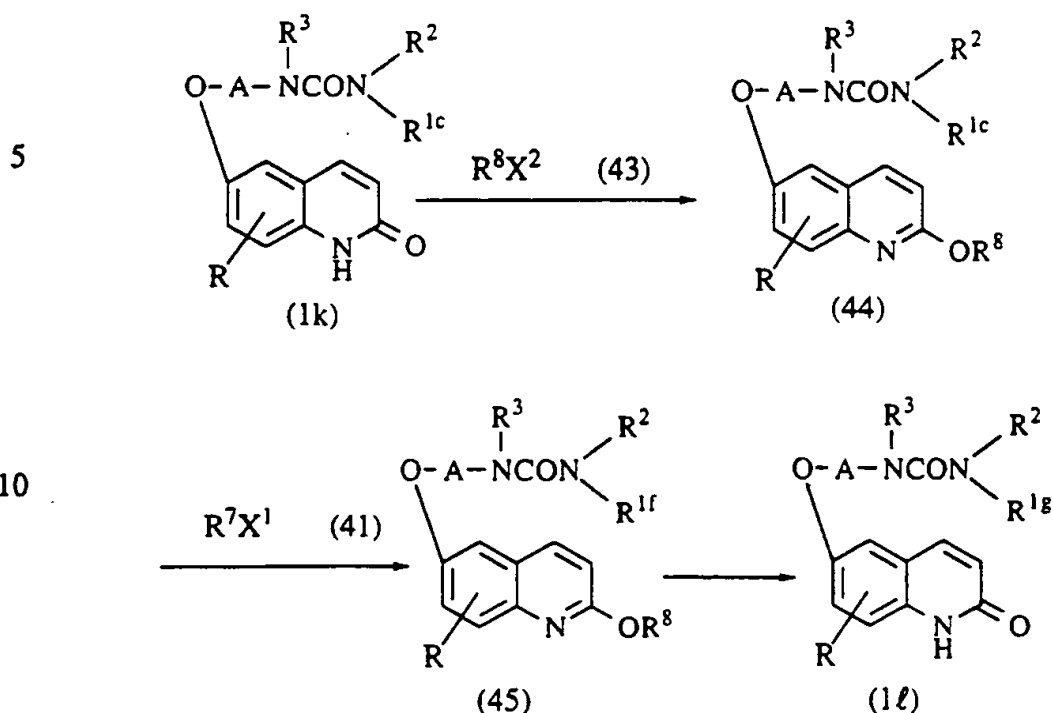
wherein R, R², R³, R^{1c}, A, X¹ and the bond between 3- and 4-positions of the carbostyryl nucleus are the same as defined above, R^{1f} is a cycloalkyl group
 15 having a tetrahydropyranyloxy-lower alkoxy substituent, R⁷ is a tetrahydro-
 pyranyloxy-lower alkyl group, and R^{1g} is a cycloalkyl group having a hydroxy-
 substituted lower alkoxy substituent.

The reaction of the compound (1k) and the compound (41) is carried out
 under the same conditions as those in the reaction of the compound (1g) and
 20 the compound (19) in the above Reaction Scheme-6.

The reaction of converting the compound (42) into the compound (1l) is
 carried out under the same conditions as those in the hydrolysis of the
 compound (1h) of the above Reaction Scheme-6. The reaction may be

preferably carried out in the presence of an acid.

Reaction Scheme-17

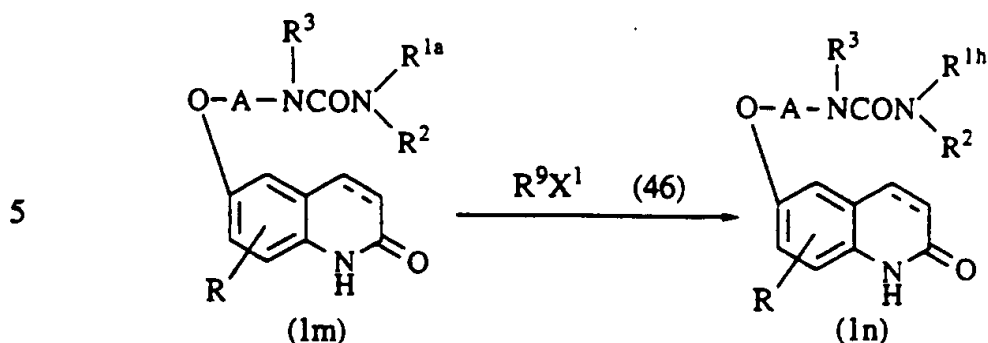


wherein R, R², R³, R^{1c}, R^{1f}, R^{1g}, R⁷, A, X¹ and X² are the same as defined above,
 and R⁸ is a lower alkoxy-lower alkyl group.

The reaction of the compound (1k) and the compound (43) is carried out under the same conditions as those in the reaction of the compound (1g) and the compound (19) in the above Reaction Scheme-6.

20 The reaction of the compound (44) and the compound (41) is carried out under the same conditions as those in the reaction of the compound (1g) and the compound (19) in the above Reaction Scheme-6.

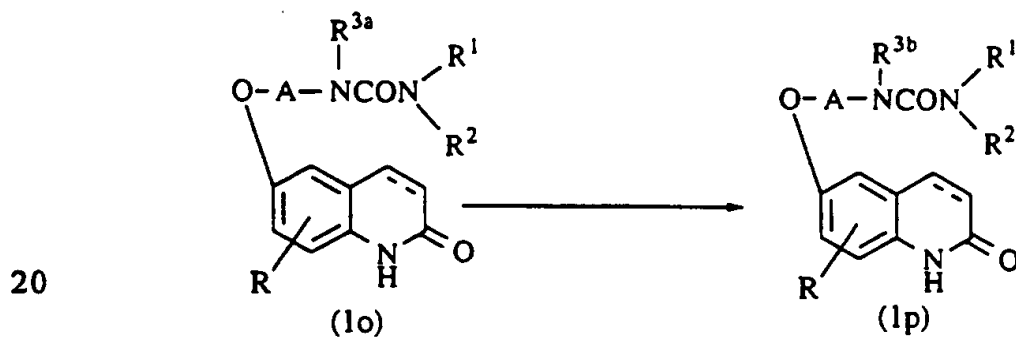
The reaction of converting the compound (45) into the compound (1l) is carried out under the same conditions as those in the reaction of converting the compound (42) into the compound (1l) in the above Reaction Scheme-16.

Reaction Scheme-18

wherein R, R², R³, R^{1a}, A, X¹ and the bond between 3- and 4-positions of the carbostyryl nucleus are the same as defined above, R^{1h} is a lower alkyl group
 10 having a substituent selected from a lower alkoxy group and a phenyl-lower alkoxy group, and R⁹ is a lower alkyl group or a phenyl-lower alkyl group.

The reaction of the compound (1m) and the compound (46) is carried out under the same conditions as those in the reaction of the compound (1e) and the compound (19) in the above Reaction Scheme-6.

15 Reaction Scheme-19

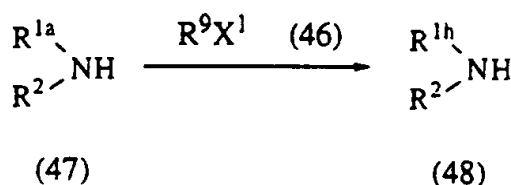


wherein R, R¹, R², A and the bond between 3- and 4-positions of the carbostyryl nucleus are the same as defined above, R^{3a} is a lower alkenyl group, and R^{3b} is a

lower alkyl group.

The reduction reaction of the compound (1o) to convert into the compound (1p) is carried out under the same conditions as those in the reaction of converting the compound (27) into the compound (8) by using a catalyst in
5 the above Reaction Scheme-7.

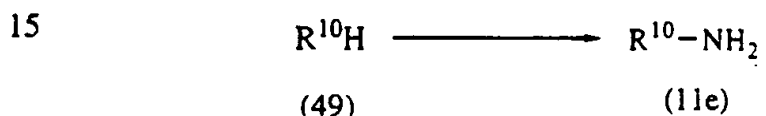
Reaction Scheme-20



10 wherein R^{1a} , R^2 , R^{1h} , R^9 and X^1 are the same as defined above.

The reaction of the compound (47) and the compound (46) is carried out under the same conditions as those in the reaction of the compound (1e) and the compound (19) in the above Reaction Scheme-6.

Reaction Scheme-21



wherein R^{10} is an amino group having optionally a substituent selected from a lower alkyl group and a cycloalkyl group.

The reaction of converting the compound (49) into the compound (11e)
20 is carried out by reacting the compound (49) with a metal nitrite such as sodium nitrite, potassium nitrite, in a suitable solvent such as water, in the presence of an acid, and then reacting the product with formamidine sulfinic acid in the presence of a basic compound in a suitable solvent.

The acid used in the reaction with the metal nitrite is, for example, hydro-

chloric acid, hydrobromic acid, sulfuric acid, tetrafluoroboric acid, hexafluorophosphoric acid, etc. The reaction is usually carried out at a temperature from room temperature to 150°C, preferably at a temperature from room temperature to about 100°C, for 1 hour to about 5 hours. The metal nitrite is usually used in
5 an amount of 1 mole to 5 moles, preferably in an amount of 1 mole to 3 moles, to 1 mole of the compound (49).

The solvent and the basic compound used in the reaction with the formamidine sulfinic acid are the same solvents and the same basic compounds as those in the reaction of the compound (4) and the compound (5) in the
10 above Reaction Scheme-2. The reaction is usually carried out at a temperature from room temperature to 150°C, preferably at a temperature from room temperature to about 100°C, for one hour to about 5 hours. The formamidine sulfinic acid is usually used in an amount of 1 mole to 5 moles, preferably in an amount of 1 mole to 3 moles, to 1 mole of the compound (49).

15 The compound of the formula (11) wherein at least one of R¹ and R² is a lower alkyl group having a hydroxy substituent or a cycloalkyl group having a hydroxy substituent can be converted into an optically active compound (11) by reacting with an optically active compound in the presence of an acid in a suitable solvent to give an adduct compound wherein a hydroxy group of the
20 formula (11) is combined with the optionally active compound, followed by hydrolyzing the resulting compound, or by subjecting the compound (11) to optical resolution by reacting with an optically active compound in a suitable solvent. The solvent includes, for example, alcohols (e.g. methanol, ethanol, isopropanol, etc.), aromatic hydrocarbons (e.g. benzene, toluene, xylene, etc.),

halogenated hydrocarbons (e.g. dichloromethane, dichloroethane, chloroform, carbon tetrachloride, etc.), ethers (e.g. diethyl ether, dioxane, tetrahydrofuran, diglyme, etc.), saturated hydrocarbons (e.g. n-hexane, n-heptane, cyclohexane, etc.), ketones (e.g. acetone, methyl ethyl ketone, etc.), polar solvents (e.g. 5 dimethylformamide, dimethyl sulfoxide, hexamethylphosphoric triamide, acetonitrile, etc.), or a mixture thereof. The acid includes, for example, mineral acids (e.g. hydrochloric acid, sulfuric acid, hydrobromic acid, etc.), organic acids (e.g. formic acid, acetic acid, methanesulfonic acid, p-toluenesulfonic acid, etc.), etc. The optically active compound may be optically active acids, for example, 10 (+)- and (-)-tartaric acid, (+)- and (-)-di-p-toluoyltartaric acid, (+)- and (-)-malic acid, (+)- and (-)-mandelic acid, D- or L-camphor-10-sulfonic acid, etc. The optically active compound is usually used at least in an equimolar amount, preferably in an amount of 1 mole to 1.5 mole, to 1 mole of the starting compound. The reaction is usually carried out at a temperature from room 15 temperature to 200°C, preferably at a temperature from room temperature to about 150°C, for one hour to about 10 hours. The subsequent hydrolysis is carried out under the same conditions as those in the hydrolysis of the compound (1f) in the above Reaction Scheme-6.

The optical resolution of the compound (11) is carried out, for example, 20 by reacting with an optically active compound in a suitable solvent to give a salt of the compound (11), fractional crystallization of the salt, and then followed by desaltation of the resulting optically active salt of the compound (11). The optically active compound to be used for salt-formation of the compound (11) may be any compound being capable to form a salt with the

compound (11), for example, the above mentioned optically active compounds. The solvent may be any solvent which is conventionally used in a conventional optical resolution, for example, the same solvents as those for the above reaction of the hydroxy group of the compound (11) and the optically active compound.

- 5 The optically active compound is usually used in an amount of 0.3 mole to 3 moles, preferably in an amount of 0.5 mole to 1 mole, to 1 mole of the compound (11). The reaction is usually carried out at a temperature from 0°C to about 100°C, preferably at a temperature from room temperature to about 50°C.

- 10 The fractional crystallization of the salt of the compound (11) is carried out by a conventional method to isolate the salt of the optically active compound (11).

- The subsequent desaltation of the salt of the optically active compound (11) is carried out in the presence of a basic compound in a suitable solvent. The solvent includes, for examples, in addition to water, the same solvents as those in the above salt-formation reaction. The basic compound includes, for
15 example, inorganic bases such as sodium hydroxide, sodium carbonate, potassium hydroxide, potassium carbonate, potassium hydrogen carbonate, sodium hydrogen carbonate, etc. The basic compound may be used in a largely excess amount.

- 20 Among the carbostyryl derivatives (1) of the present invention, the compounds having an acidic group can easily be converted into salts by treating with a pharmaceutically acceptable basic compound. The basic compound includes, for example, sodium hydroxide, potassium hydroxide, calcium hydroxide, sodium carbonate, potassium hydrogen carbonate, etc.

The compounds of the present invention obtained in the above processes can easily be isolated and purified by conventional isolation methods. The isolation methods are, for example, extraction with a solvent, dilution method, recrystallization method, column chromatography, preparative thin
5 layer chromatography, and the like.

The present invention also includes geometrical isomers, optical isomers, as well.

The desired compounds (1) of the present invention and salts thereof are used in the form of a conventional pharmaceutical preparation. The preparation
10 is prepared by using conventional diluents or carriers such as fillers, thickening agents, binders, wetting agent, disintegrators, surfactants, lubricants, etc. The pharmaceutical preparations can be selected from various forms in accordance with the desired utilities, and the representative forms are tablets, pills, powders, solutions, suspensions, emulsions, granules, capsules, suppositories, injections
15 (solutions, suspensions, etc.), etc. In order to form in tablets, there are used conventional carriers such as vehicles (e.g. lactose, white sugar, sodium chloride, glucose, urea, starch, calcium carbonate, kaolin, crystalline cellulose, silicic acid, etc.), binders (e.g. water, ethanol, propanol, simple syrup, glucose solution, starch solution, gelatin solution, carboxymethyl cellulose, shellac, methyl
20 cellulose, potassium phosphate, polyvinylpyrrolidone, etc.), disintegrators (e.g. dry starch, sodium alginate, agar powder, laminaran powder, sodium hydrogen carbonate, calcium carbonate, polyoxyethylene sorbitan fatty acid esters, sodium laurylsulfate, stearic monoglyceride, starches, lactose, etc.), disintegration inhibitors (e.g. white sugar, stearin, cacao butter, hydrogenated oils, etc.),

absorption promoters (e.g. quaternary ammonium base, sodium laurylsulfate, etc.), wetting agents (e.g. glycerin, starches, etc.), adsorbents (e.g. starches, lactose, kaolin, bentonite, colloidal silicates, etc.), lubricants (e.g. purified talc, stearates, boric acid powder, polyethylene glycol, etc.), etc. Moreover, the

5 tablets may also be in the form of a conventional coated tablet, such as sugar-coated tablets, gelatin-coated tablets, enteric coated tablets, film coating tablets, or double or multiple layer tablets. In the preparation of pills, the carriers include vehicles (e.g. glucose, lactose, starches, cacao butter, hydrogenated vegetable oils, kaolin, talc, etc.), binders (e.g. gum arabic powder, tragacanth

10 powder, gelatin, ethanol, etc.), disintegrators (e.g. laminaran, agar, etc.), etc. In the preparation of suppositories, the carriers include, for example, polyethylene glycol, cacao butter, higher alcohols, higher alcohol esters, gelatin, semi-synthetic glycerides, etc. Capsules can be prepared by charging a mixture of the compound of the present invention and the above carriers into hard gelatin

15 capsules or soft capsules in usual manner. In the preparation of injections, the solutions, emulsions and suspensions are sterilized and are preferably made isotonic with the blood. In the preparation of these solutions, emulsions and suspensions, there are used conventional diluents such as water, ethyl alcohol, propylene glycol, ethoxylated isostearyl alcohol, polyoxylated isostearyl

20 alcohol, polyoxyethylene sorbitan fatty acid esters, etc. In this case, the pharmaceutical preparations may also be incorporated with sodium chloride, glucose, or glycerin in an amount sufficient to make them isotonic, and may also be incorporated with conventional solubilizers, buffers, anesthetizing agents. Besides, the pharmaceutical preparations may optionally be incorporated with

coloring agents, preservatives, perfumes, flavors, sweetening agents, and other medicaments, if required.

The amount of the desired compound (1) of the present invention to be incorporated into the pharmaceutical preparation is not specified but may be
5 selected from a broad range, but usually, it is preferably in the range of 1 to 70 % by weight, more preferably 1 to 30 % by weight.

The pharmaceutical preparation containing as an active ingredient the compounds (1) of the present invention and a salt thereof may be administered by any method, and suitable method for administration may be determined in
10 accordance with various forms of preparations, ages, sexes and other conditions of the patients, the degree of severity of diseases, etc. For example, tablets, pills, solutions, suspensions, emulsions, granules and capsules are administered orally. The injections are intravenously administered alone or together with a conventional auxiliary liquid (e.g. glucose, amino acid solutions, etc.), and
15 further are optionally administered alone in intramuscular, intracutaneous, subcutaneous, or intraperitoneal route, if required. Suppositories are administered in intrarectal route.

The dosage of the pharmaceutical preparation of the present invention may be selected in accordance with the usage, ages, sexes and other conditions
20 of the patients, the degree of severity of the diseases, etc., but it is usually in the range of about 0.1 to 10 mg of the active compound (1) of the present invention per 1 kg of body weight of the patient per day. The active compound is preferably contained in an amount of about 1 to about 200 mg per the dosage unit.

Best Mode for Carrying Out the Invention

The present invention is illustrated in more detail by the following Preparations of pharmaceutical preparations, Reference Examples of processes for preparing the starting compounds to be used for preparing the desired compounds (1) of the present invention, and Examples of processes for preparing the desired compounds (1), and Pharmacological Experiments of the activities of the desired compounds of the present invention.

Preparation 1

Preparation of tablets:

10	<u>Components</u>	<u>Amount</u>
	6-{3-[3-(trans-2-Hydroxycyclohexyl)-3-cyclopropylureido]propoxy}carbostyryl	5 g
	Lactose (Japanese Pharmacopeia)	50 g
	Corn starch (Japanese Pharmacopeia)	25 g
15	Crystalline cellulose (Japanese Pharmacopeia)	25 g
	Methyl cellulose (Japanese Pharmacopeia)	1.5 g
	Magnesium stearate (Japanese Pharmacopeia)	1 g

The active compound of the present invention, lactose, corn starch and crystalline cellulose are mixed. The mixture is granulated with a 5 % aqueous solution of methyl cellulose. The resulting particles are passed through a screen (200 mesh) and dried carefully. The mixture is tabletted by a conventional manner to give 1000 tablets.

Preparation 2

Preparation of capsules:

	<u>Components</u>	<u>Amount</u>
	6-[3-(1,3-Dimethyl-3-cyclohexylureido)-propoxy]carbostyryl	10 g
	Lactose (Japanese Pharmacopeia)	80 g
5	Starch (Japanese Pharmacopeia)	30 g
	Talc (Japanese Pharmacopeia)	5 g
	Magnesium stearate (Japanese Pharmacopeia)	1 g

The above components are mixed, pulverized and stirred well. The resulting uniform mixture is charged into gelatin capsules for oral administration
10 of a desired size to give 1000 capsules.

Preparation 3

Preparation of injection preparation:

	<u>Components</u>	<u>Amount</u>
15	6-{3-Cyclohexyl-[3-(2-acetyloxybutyl)ureido]-propoxy}carbostyryl	1 g
	Polyethylene glycol (molecular weight: 4000) (Japanese Pharmacopeia)	0.3 g
	Sodium chloride (Japanese Pharmacopeia)	0.9 g
20	Polyoxyethylene sorbitan monooleate (Japanese Pharmacopeia)	0.4 g
	Sodium metabisulfite	0.1 g
	Methyl-paraben (Japanese Pharmacopeia)	0.18 g
	Propyl-paraben (Japanese Pharmacopeia)	0.02 g
	Distilled water for injection	100 ml

25 The above parabens, sodium metabisulfite and sodium chloride are dissolved in distilled water of half volume of the above with stirring at 80°C.

The solution thus obtained is cooled to 40°C, and the active compound of the present invention and further polyethylene glycol and polyoxyethylene sorbitan monooleate are dissolved in the above solution. To the solution is added distilled water for injection to adjust to the desired volume, and the solution is sterilized by filtering with an appropriate filter paper to give an injection preparation.

Reference Example 1

A suspension of 6-hydroxycarbostyryl (300 g) and potassium carbonate (308 g) in dimethylformamide (2 liters) is heated with stirring at 70-80°C for one hour. To the suspension is added N-(3-bromopropyl)phthalimide (498 g), and the mixture is further stirred at the same temperature for 9 hours. The reaction solution is poured into ice-water, and the precipitated crystals are collected by filtration, washed successively with water, ethanol and diethyl ether, and dried to give 6-(3-phthalimidopropoxy)carbostyryl (410 g) as a white powder.

¹H-NMR (DMSO-d₆) δ ppm: 2.00-2.18 (2H, m), 3.78 (2H, t, J=6 Hz), 4.04 (2H, t, J=6 Hz), 6.47 (1H, d, J=9.5 Hz), 6.97 (1H, dd, J=2.5 Hz, J=9 Hz), 7.10 (1H, d, J=2.5 Hz), 7.18 (1H, d, J=9 Hz), 7.78 (1H, d, J=9.5 Hz), 7.75-7.94 (5H, m), 12.08 (1H, brs)

Reference Example 2

To a suspension of 6-(3-phthalimidopropoxy)carbostyryl (300 g) in ethanol (3 liters) is added hydrazine monohydrate (46 g), and the mixture is refluxed for 8 hours. After the mixture is allowed to cool, the precipitated crystals are collected by filtration, suspended in water, and the suspension thus obtained is acidified with conc. hydrochloric acid, and stirred for one hour. The

insoluble materials are removed by filtration, and the filtrate is concentrated under reduced pressure to remove the solvent. The residue is neutralized to pH 7 with a 15 % aqueous sodium hydroxide solution. The precipitated crystals are collected by filtration, and washed successively with ethanol and diethyl ether, and dried to give 6-(3-aminopropoxy)carbostyryl (140 g) as a white powder.

$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 2.02-2.20 (2H, m), 2.88-3.08 (2H, m), 4.12 (2H, t, $J=6$ Hz), 6.52 (1H, d, $J=9.5$ Hz), 7.18 (1H, dd, $J=2.5$ Hz, $J=9$ Hz), 7.24 (1H, d, $J=2.5$ Hz), 7.32 (1H, d, $J=9$ Hz), 7.86 (1H, d, $J=9.5$ Hz), 8.15-8.50 (3H, m), 11.75 (1H, brs)

10 Reference Example 3

To a solution of N,N-carbonyldiimidazole (139 g) and imidazole (117 g) in dimethylsulfoxide (2 liters) is added with stirring 6-(3-aminopropoxy)carbostyryl (200 g) in portions under ice-cooling. The mixture is further stirred at room temperature for one day, and poured into ice-water. The precipitated crystals are collected by filtration, and washed with water. The crystals thus obtained are further washed successively with ethanol and diethyl ether, and dried to give 6-[3-(1-imidazolyl)carbonylaminopropoxy]carbostyryl (162 g) as a white powder.

$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 1.94-2.18 (2H, m), 3.30-3.63 (2H, m), 4.09 (2H, t, $J=6$ Hz), 6.51 (1H, d, $J=9.5$ Hz), 7.05 (1H, s), 7.15 (1H, dd, $J=2.5$ Hz, $J=9$ Hz), 7.22 (1H, d, $J=2.5$ Hz), 7.26 (1H, d, $J=9$ Hz), 7.69 (1H, s), 7.84 (1H, d, $J=9.5$ Hz), 8.26 (1H, s), 8.61 (1H, t, $J=5.3$ Hz), 11.68 (1H, brs)

Reference Example 4

To a suspension of 6-hydroxycarbostyryl (50 g) and 1-bromo-3-chloro-

propane (120 ml) in dimethylformamide (600 ml) is added potassium carbonate (65 g) in portions at room temperature. The mixture is stirred at room temperature for three days, and the insoluble materials are collected by filtration and washed with n-hexane. The resulting crystals are further washed
5 successively with water, acetone and n-hexane, and dried to give 6-(3-chloropropoxy)carbostyryl (50.7 g) as a white powder.

$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 2.19 (2H, quint, $J=6$ Hz), 3.81 (2H, t, $J=6$ Hz), 4.11 (2H, t, $J=6$ Hz), 6.50 (1H, d, $J=9.5$ Hz), 7.16 (1H, dd, $J=2.5$ Hz, $J=9$ Hz), 7.20-7.32 (2H, m), 7.84 (1H, d, $J=9.5$ Hz), 11.60 (1H, br)

10 Reference Example 5

A suspension of 6-(3-chloropropoxy)carbostyryl (170 g) and sodium iodide (129.5 g) in dimethylformamide (1.7 liter) is heated with stirring at 60°C for one hour. To the mixture is added potassium phthalimide (159 g), and the mixture is heated with stirring at 70°C for 6 hours. After the mixture is allowed
15 to cool, the precipitated crystals are collected by filtration, and washed with water. The mixture is further washed successively with ethanol and diethyl ether, and dried to give 6-(3-phthalimidopropoxy)carbostyryl (222 g) as a white powder.

$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 2.00-2.18 (2H, m), 3.78 (2H, t, $J=6$ Hz), 4.04
20 (2H, t, $J=6$ Hz), 6.47 (1H, d, $J=9.5$ Hz), 6.97 (1H, dd, $J=2.5$ Hz, $J=9$ Hz), 7.10 (1H, d, $J=2.5$ Hz), 7.18 (1H, d, $J=9$ Hz), 7.78 (1H, d, $J=9.5$ Hz), 7.75-7.94 (5H, m), 12.08 (1H, brs)

Reference Example 6

A suspension of 6-(3-chloropropoxy)carbostyryl (100 g) and sodium

azide (33 g) in dimethylformamide is refluxed at 80°C for 4 hours. After the mixture is allowed to cool, to the mixture is added ice-water, and the precipitated crystals are collected by filtration, washed with diethyl ether, and dried to give 6-(3-azidopropoxy)carbostyryl (100 g) as a white powder.

5 ¹H-NMR (DMSO-d₆) δ ppm: 2.00 (2H, quint, J=6 Hz), 3.53 (2H, t, J=6 Hz), 4.06 (2H, t, J=6 Hz), 6.51 (1H, d, J=9.5 Hz), 7.12-7.35 (3H, m), 7.85 (1H, d, J=9.5 Hz), 11.69 (1H, s)

Reference Example 7

To a solution of 6-(3-azidopropoxy)carbostyryl (17.5 g) in a mixture of ethyl acetate-methanol (1:1, 700 ml) is added 10 % palladium-carbon (1.75 g), and the mixture is subjected to hydrogenation at room temperature under atmospheric pressure. After the reaction is complete, the catalyst is removed by filtration, and the filtrate is concentrated under reduced pressure to remove the solvent. The resulting residue is washed with diethyl ether to give 6-(3-amino-
15 propoxy)carbostyryl (14.7 g) as a white powder.

¹H-NMR (DMSO-d₆) δ ppm: 2.02-2.20 (2H, m), 2.88-3.08 (2H, m), 4.12 (2H, t, J=6 Hz), 6.52 (1H, d, J=9.5 Hz), 7.18 (1H, dd, J=2.5 Hz, J=9 Hz), 7.24 (1H, d, J=2.5 Hz), 7.32 (1H, d, J=9 Hz), 7.86 (1H, d, J=9.5 Hz), 8.15-8.50 (3H, m), 11.75 (1H, brs)

20 Reference Example 8

To a suspension of lithium aluminum hydride (1.9 g) in anhydrous tetrahydrofuran (50 ml) is added dropwise with stirring a solution of 6-(3-azidopropoxy)carbostyryl (10 g) in anhydrous tetrahydrofuran (200 ml) under ice-cooling. The mixture is stirred at room temperature for one hour, and thereto are

added dropwise water (2 ml), a 15 % aqueous sodium hydroxide solution (2 ml) and water (6 ml). The insoluble materials are collected by filtration, and added to a mixture of chloroform-methanol (8:1). The mixture is heated, and then cooled. The insoluble material are removed by filtration. The filtrate is
5 concentrated under reduced pressure to remove the solvent, and thereto is added diethyl ether. The precipitated crystals are collected by filtration to give 6-(3-aminopropoxy)carbostyryl (6.2 g) as a white powder.

$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 2.02-2.20 (2H, m), 2.88-3.08 (2H, m), 4.12 (2H, t, $J=6$ Hz), 6.52 (1H, d, $J=9.5$ Hz), 7.18 (1H, dd, $J=2.5$ Hz, $J=9$ Hz), 7.24 (1H, d, $J=2.5$ Hz), 7.32 (1H, d, $J=9$ Hz), 7.86 (1H, d, $J=9.5$ Hz), 8.15-8.50 (3H, m),
10 11.75 (1H, brs)

Reference Example 9

Cyclohexene oxide (143 ml) and cyclopropylamine (82 g) are dissolved in methanol (1 liter), and the mixture is refluxed for 5 hours. The mixture is
15 concentrated under reduced pressure to remove the solvent, and the resulting residue is distilled under reduced pressure to give trans-N-(2-hydroxycyclohexyl)-N-cyclopropylamine (126 g) as a colorless oil.

B.p. 79-85°C/0.5-1 mmHg

Reference Example 10

20 To toluene (1.5 liter) are added trans-N-(2-hydroxycyclohexyl)-N-cyclopropylamine (150 g), (R)-(-)-mandelic acid (147 g) and p-toluenesulfonic acid monohydrate (203 g), and the mixture is refluxed for 6 hours during which the generated water is removed by a Dean-stark apparatus. The mixture is poured into ice-water, and thereto is added an aqueous solution of sodium hydrogen

carbonate (98 g), and the mixture is stirred for one hour. The toluene layer is collected, and the aqueous layer is extracted with ethyl acetate. The organic layers are combined, washed with a saturated aqueous sodium chloride solution, and dried over anhydrous sodium sulfate. The mixture is concentrated under
5 reduced pressure to remove the solvent, and the residue is purified by silica gel column chromatography (solvent; n-hexane:ethyl acetate = 3:1 → 1:1), and crystallized from ethyl acetate-n-hexane (1:1). The resultant is further recrystallized from ethyl acetate-n-hexane (1:2) to give (S,S)-(+)-trans-N-(2-mandeloyloxycyclohexyl)-N-cyclopropylamine (25 g) as colorless rods.

10 M.p. 102-103°C

Reference Example 11

(S)-(+)-Mandelic acid is treated in the same manner as in Reference Example 10 to give (R,R)-(-)-trans-N-(2-mandeloyloxycyclohexyl)-N-cyclopropylamine, which is recrystallized from ethyl acetate-n-hexane (1:2) to give
15 colorless rods.

M.p. 101-103°C

Reference Example 12

To a suspension of (S,S)-(+)-trans-N-(2-mandeloyloxycyclohexyl)-N-cyclopropylamine (25 g) in methanol (250 ml) is added dropwise with stirring a
20 3N aqueous potassium hydroxide solution (87 ml) at room temperature. The mixture is further stirred at room temperature for 0.5 hour, and extracted with methylene chloride. The extract is washed successively with water and a saturated aqueous sodium chloride solution, and dried over anhydrous sodium sulfate. The resultant is concentrated under reduced pressure, and distilled

under reduced pressure to give (S,S)-(+)-trans-N-(2-hydroxycyclohexyl)-N-cyclopropylamine (13.4 g) as a colorless oil.

B.p. 87°C/2 mmHg

After being allowed to stand, the above product is crystallized as
5 colorless rods.

M.p. 43-45°C

$[\alpha]_D^{24} = +59.4^\circ$ (c=1.0, methanol)

Reference Example 13

(R,R)-(-)-trans-N-(2-Mandeloyloxycyclohexyl)-N-cyclopropylamine is
10 treated in the same manner as in Reference Example 12 to give (R,R)-(-)-trans-N-(2-hydroxycyclohexyl)-N-cyclopropylamine as a colorless oil.

B.p. 79°C/0.5 mmHg

The above product is allowed to stand to give colorless rods.

M.p. 43-45°C

15 $[\alpha]_D^{24} = -59.3^\circ$ (c=1.0, methanol)

Reference Example 14

1-Amino-2-butanol (120 g) is added dropwise into a solution of cyclohexanone (132 g) in ethanol (600 ml) at room temperature, and the mixture is stirred at room temperature for one day. To the reaction solution is added 10%
20 palladium-carbon (6 g), and the mixture is subjected to catalytic hydrogenation at 60°C under 4 atms of hydrogen gas. The catalyst is removed by filtration, and the filtrate is concentrated under reduced pressure, and distilled under reduced pressure to give N-(2-hydroxybutyl)-N-cyclohexylamine (223 g) as a colorless oil.

B.p. 87-93°C/0.35-0.4 mmHg

Reference Example 15

To methanol (200 ml) are added 1,2-epoxybutane (72.2 g) and cyclohexylamine (99.2 g), and the mixture is refluxed for 6 hours. The mixture is concentrated under reduced pressure to remove the solvent to give N-(2-hydroxybutyl)-N-cyclohexylamine (105 g) as a colorless oil.

B.p. 87-93°C/0.35-0.4 mmHg

Reference Example 16

To a solution of triphosgene (4.35 g) in toluene (70 ml) is added dropwise N-methylcyclohexylamine (5 g). To the mixture is added dropwise pyridine (3.5 g), and the mixture is refluxed for 4 hours. The mixture is allowed to cool, and the organic layer is separated, washed with 0.1 N hydrochloric acid, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to remove the solvent to give N-methyl-N-cyclohexylaminocarbonyl chloride (7.62 g) as a colorless oil.

¹H-NMR (CDCl₃) δ ppm: 1.00-2.00 (10H, m), 2.9 and 3.1 (all 3H, each s), 4.10 (1H, m)

Reference Example 17

6-(3-Chloropropoxy)carbostyryl (20 g) is added into a 40 % solution of methylamine in methanol (200 ml), and the mixture is heated with stirring at 100°C overnight in a sealed tube. The mixture is concentrated under reduced pressure to remove the solvent, and the precipitated crystals are washed with a mixture of chloroform-diethyl ether, purified by silica gel column chromatography (solvent; methylene chloride:methanol:aqueous ammonia = 50:10:1), and

recrystallized from chloroform-diethyl ether to give 6-(3-methylaminopropoxy)-carbostyryl (15.4 g).

M.p. 160-161.5°C

Reference Example 18

5 Using the corresponding starting compounds, the following compounds are obtained in the same manner as in Reference Example 17.

(1) 6-(3-Ethylaminopropoxy)carbostyryl

¹H-NMR (DMSO-d₆) δ ppm: 1.08 (3H, t, J=7 Hz), 1.85-2.05 (2H, m), 2.72 (2H, q, J=7 Hz), 2.83 (2H, t, J=7 Hz), 4.06 (2H, t, J=6 Hz), 6.50 (1H, d, J=9.5 Hz),
10 7.10-7.30 (3H, m), 7.84 (1H, d, J=9.5 Hz)

(2) 6-(3-Allylaminopropoxy)carbostyryl

¹H-NMR (DMSO-d₆) δ ppm: 2.15-2.20 (2H, m), 3.03 (2H, t, J=7 Hz), 3.59 (2H, d, J=6.5 Hz), 4.09 (2H, t, J=6 Hz), 5.35-5.55 (2H, m), 5.85-6.05 (1H, m), 6.50 (1H, d, J=9.5 Hz), 7.10-7.30 (3H, m), 7.84 (1H, d, J=9.5 Hz)

15 Reference Example 19

6-Hydroxycarbostyryl (100 g) is added into phosphorus oxychloride (500 ml), and the mixture is refluxed for 5 hours. The mixture is concentrated under reduced pressure to remove the phosphorus oxychloride, and the residue thus obtained is dissolved in a small amount of chloroform, and then the mixture
20 is poured into ice-water. The precipitated crystals are collected by filtration, washed successively with water, acetone and n-hexane, and dried to give 2-chloro-6-hydroxyquinoline-hydrochloride (127 g).

¹H-NMR (DMSO-d₆) δ ppm: 7.50-7.70 (2H, m), 7.78 (1H, s), 7.95 (1H, d,

J=9 Hz), 8.43 (1H, d, J=9 Hz)

Reference Example 20

To a suspension of 2-chloro-6-hydroxycarbostyryl-hydrochloride (25 g) and potassium carbonate (38 g) in dimethylformamide (600 ml) is added N-(3-bromopropyl)phthalimide (31 g). The mixture is heated with stirring at 60°C overnight. The reaction solution is poured into ice-water, and the precipitated crystals are collected by filtration, washed with water, and dried to give 2-chloro-6-(3-phthalimidopropoxy)quinoline (19.3 g) as a white powder.

¹H-NMR (DMSO-d₆) δ ppm: 2.10-2.25 (2H, m), 3.82 (2H, t, J=7 Hz), 4.17 (2H, t, J=6 Hz), 7.23 (1H, dd, J=3 Hz, J=9 Hz), 7.36 (1H, d, J=3 Hz), 7.52 (1H, d, J=9 Hz), 7.80 (1H, d, J=9 Hz), 7.85 (4H, s), 8.28 (1H, d, J=9 Hz)

Reference Example 21

To a suspension of 2-chloro-6-(3-phthalimidopropoxy)quinoline (9.0 g) in ethanol (250 ml) is added hydrazine-monohydrate (1.4 g), and the mixture is refluxed for 7.5 hours. The mixture is allowed to cool, and the precipitated crystals are collected by filtration, and suspended in water. The mixture is acidified with conc. hydrochloric acid, and stirred for one hour. The mixture is basified with a 10 % aqueous potassium hydroxide solution, and extracted with chloroform. The extract is dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to remove the solvent to give 2-chloro-6-(3-aminopropoxy)quinoline (4.7 g) as a white powder.

¹H-NMR (DMSO-d₆) δ ppm: 1.80-1.95 (2H, m), 2.74 (2H, t, J=7 Hz), 4.18 (2H, t, J=6 Hz), 7.40-7.50 (2H, m), 7.53 (1H, d, J=9 Hz), 7.86 (1H, d, J=10 Hz), 8.32 (1H, d, J=9 Hz)

Reference Example 22

To a solution of N,N-carbonyldimidazole (2.1 g) and imidazole (1.9 g) in chloroform (100 ml) is added dropwise with stirring a solution of 2-chloro-6-(3-aminopropoxy)quinoline (3 g) in chloroform (40 ml) at -10°C . The mixture is stirred at room temperature overnight, and thereto is added dropwise a solution of N-(2-hydroxybutyl)-N-cyclohexylamine (2.9 g) in chloroform (10 ml). The mixture is stirred at room temperature for one hour, and refluxed for 2.5 hours. The mixture is allowed to cool, and the chloroform layer is washed successively with diluted hydrochloric acid, water and a saturated aqueous sodium hydrogen carbonate solution, dried over anhydrous magnesium sulfate, and evaporated to remove the solvent to give 2-chloro-6-{3-[3-cyclohexyl-3-(2-hydroxybutyl)-ureido]propoxy}quinoline (6.8 g) as a colorless oil.

$^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ ppm: 0.87 (3H, t, $J=7$ Hz), 0.90-1.85 (11H, m), 1.90-2.05 (2H, m), 2.95-3.10 (2H, m), 3.15-3.30 (2H, m), 3.35-3.50 (1H, m), 3.65-3.90 (1H, m), 4.14 (2H, t, $J=6$ Hz), 5.49 (1H, d, $J=4$ Hz), 6.76 (1H, t, $J=5$ Hz), 7.40-7.60 (3H, m), 7.86 (1H, d, $J=9$ Hz), 8.31 (1H, d, $J=9$ Hz)

Reference Example 23

To a solution of 2-chloro-6-{3-[3-cyclohexyl-3-(2-hydroxybutyl)ureido]propoxy}quinoline (6.3 g), 4-dimethylaminopyridine (0.1 g) and triethylamine (2.3 g) in methylene chloride (80 ml) is added dropwise with stirring acetic anhydride (1.8 g) at room temperature. The methylene chloride layer is washed successively with diluted hydrochloric acid, water and a saturated aqueous sodium hydrogen carbonate solution, and dried over anhydrous magnesium sulfate. The resultant is concentrated under reduced pressure to remove the

solvent to give 2-chloro-6-{3-[3-cyclohexyl-3-(2-acetyloxybutyl)ureido]-propoxy}quinoline (6.7 g) as a colorless oil.

¹H-NMR (DMSO-d₆) δ ppm: 0.81 (3H, t, J=7 Hz), 0.90-1.80 (11H, m),
1.80-2.10 (5H, m), 3.00-3.45 (4H, m), 3.55-3.70 (1H, m), 4.13 (2H, t, J=6 Hz),
5 4.35-5.00 (1H, m), 6.34 (1H, t, J=5 Hz), 7.35-7.60 (3H, m), 7.86 (1H, d, J=9 Hz),
8.31 (1H, d, J=9 Hz)

Reference Example 24

To a solution of 2-chloro-6-{3-[3-cyclohexyl-3-(2-acetyloxybutyl)-ureido]propoxy}quinoline (5.6 g) in dimethylformamide (80 ml) is added sodium
10 hydride (60 % oily, 0.8 g), and the mixture is stirred at room temperature for one
hour. To the reaction solution is added methyl iodide (1.1 ml), and the mixture is
stirred for one hour. To the mixture is further added methyl iodide (2 ml), and
the mixture is stirred at room temperature overnight. The reaction solution is
poured into water, and extracted with ethyl acetate. The ethyl acetate layer is
15 separated, washed with water, and dried over anhydrous magnesium sulfate.
The resultant is concentrated under reduced pressure to remove the solvent, and
the residue is purified by silica gel column chromatography (solvent; methylene
chloride:methanol = 20:1) to give 2-chloro-6-{3-[1-methyl-3-cyclohexyl-3-(2-
acetyloxybutyl)ureido]propoxy}quinoline (5.5 g) as a colorless oil.

20 ¹H-NMR (DMSO-d₆) δ ppm: 0.79 (3H, t, J=7 Hz), 0.90-1.85 (11H, m),
1.90-2.15 (5H, m), 2.75 (3H, s), 2.80-2.95 (1H, m), 3.00-3.45 (5H, m), 4.10 (2H, t,
J=6 Hz), 4.65-4.80 (1H, m), 7.35-7.50 (2H, m), 7.53 (1H, d, J=9 Hz), 7.87 (1H, d,
J=10 Hz), 8.30 (1H, d, J=9 Hz)

Reference Example 25

(R,R)-(-)-6-{3-[3-(trans-2-Hydroxycyclohexyl)-3-cyclopropylureido]-propoxy}carbostyryl (10 g) and N,N-diisopropylethylamine (5.66 g) are dissolved in anhydrous methylene chloride (200 ml), and thereto is added
5 dropwise with stirring chloromethyl methyl ether (2.28 g) under ice-cooling. The mixture is stirred under ice-cooling for one hour, and the mixture is stirred at room temperature overnight. To the reaction solution is added a saturated aqueous sodium hydrogen carbonate solution, and the mixture is extracted with methylene chloride. The extract is washed successively with water and a
10 saturated sodium chloride solution, and dried over anhydrous sodium sulfate. The resultant is concentrated under reduced pressure to remove the solvent, and the residue is purified by silica gel column chromatography (solvent; methylene chloride:methanol = 50:1 → 30:1), and recrystallized from diethyl ether-petroleum ether to give (R,R)-(-)-6-{3-[3-(trans-2-hydroxycyclohexyl)-3-cyclopropylureido]propoxy}-2-methoxymethoxyquinoline (3.33 g) as a white
15 powder.

¹H-NMR (CDCl₃) δ ppm: 0.67-1.02 (4H, m), 1.15-1.40 (3H, m), 1.63-1.95 (4H, m), 2.05-2.18 (3H, m), 2.35-2.48 (1H, m), 3.39-3.83 (8H, m, with 3.58 (s)), 4.14 (2H, t, J=6 Hz), 5.66 (2H, s), 5.71 (1H, t, J=5.5 Hz), 6.94 (1H, d, J=8.5 Hz),
20 7.06 (1H, d, J=2.5 Hz), 7.25 (1H, dd, J=2.5, 9 Hz), 7.75 (1H, d, J=9 Hz), 7.94 (1H, d, J=8.5 Hz)

Reference Example 26

(R,R)-(-)-6-{3-[3-(trans-2-Hydroxycyclohexyl)-3-cyclopropylureido]-propoxy}-2-methoxymethoxyquinoline (2.83 g) is dissolved in dimethyl-

formamide (50 ml), and thereto is added sodium hydride (60 % oily dispersion, 0.383 g) at room temperature under argon atmosphere, and the mixture is stirred at room temperature for one hour. To the mixture is added 1-bromo-3-(2-tetrahydropyranyloxy)propane (2.14 g), and the mixture is heated with stirring
5 at 70-90°C for 5 hours. To the reaction solution is added water, and the mixture is extracted with ethyl acetate. The extract is washed successively with water and a saturated aqueous sodium chloride solution, and dried over anhydrous sodium sulfate. The resultant is concentrated under reduced pressure to remove the solvent, and the residue is purified by silica gel column
10 chromatography (solvent; ethyl acetate:n-hexane = 1:1) to give (R,R)-(-)-6-{3-[3-(trans-2-[3-(2-tetrahydropyranyloxy)propoxy]cyclohexyl)-3-cyclopropylureido]propoxy}-2-methoxymethoxyquinoline (1.7 g) as a white powder.

¹H-NMR (CDCl₃) δ ppm: 0.60-0.95 (4H, m), 1.02-1.47 (2H, m), 1.48-1.95
15 (14H, m), 2.02-2.26 (5H, m), 2.49-2.63 (1H, m), 3.33-3.52 (6H, m), 3.58 (3H, s), 3.60-3.96 (4H, m), 4.12 (2H, t, J=5 Hz), 4.45-4.60 (1H, m), 5.52-5.60 (1H, m), 5.67 (2H, s), 6.93 (1H, d, J=9 Hz), 7.06 (1H, d, J=2.5 Hz), 7.20-7.45 (1H, m), 7.74 (1H, d, J=9 Hz), 7.94 (1H, d, J=9 Hz)

Reference Example 27

20 The corresponding starting compounds are treated in the same manner as in Reference Example 9 to give the following compounds.

(1) trans-N-(2-Hydroxycyclohexyl)-N-cycloheptylamine

Colorless oil

B.p. 140°C/3 mmHg

(2) trans-N-(2-Hydroxycyclohexyl)-N-cyclooctylamine

White crystals

B.p. 150°C/1 mmHg

Reference Example 28

- 5 N-Cyclohexyl-N-(2-hydroxybutyl)amine (3 g) is dissolved in tetrahydrofuran (50 ml), and thereto is added with stirring sodium hydride (60 % oily dispersion, 2.1 g) under ice-cooling, and the mixture is heated with stirring at 60°C for one hour. To the reaction mixture is added dropwise with stirring ethyl bromide (2.1 g) under ice-cooling, and the mixture is stirred at room
- 10 temperature for 4 hours. Water is added to the reaction mixture, and the mixture is extracted with ethyl acetate. The extract is concentrated under reduced pressure to remove the solvent, and the residue is purified by silica gel column chromatography (solvent; methylene chloride:methanol:aqueous ammonia = 100:10:1) to give N-cyclohexyl-N-(2-ethoxybutyl)amine(1.6 g) as a colorless oil.
- 15 ¹H-NMR (CDCl₃) δ ppm: 0.90 (3H, t, J=7.5 Hz), 1.00-1.95 (11H, m), 2.35-2.45 (1H, m), 2.54-2.74 (2H, m), 3.30-3.40 (1H, m), 3.44-3.64 (2H, m)

Reference Example 29

- To a solution of N-cyclohexyl-N-(2-hydroxybutyl)amine (49.2 g) in tetrahydrofuran (1 liter) is added with stirring sodium hydride (60 % oily
- 20 dispersion, 12.6 g) in portions at 0°C. The mixture is stirred at the same temperature for one hour, and thereto is added dropwise benzyl bromide (34 ml). The mixture is stirred at room temperature overnight, and the mixture is concentrated under reduced pressure to remove the solvent. To the residue is added water, and the mixture is extracted with chloroform. The extract is dried

over anhydrous magnesium sulfate, concentrated under reduced pressure to remove the solvent, and the residue is purified by silica gel column chromatography (solvent; methylene chloride:methanol:aqueous ammonia = 200:10:1) to give N-cyclohexyl-N-(2-benzyloxybutyl)amine (25.8 g) as a colorless oil.

5 $^1\text{H-NMR}$ (CDCl_3) δ ppm: 0.94 (3H, t, $J=7.5$ Hz), 1.00-1.35 (5H, m), 1.50-1.95 (8H, m), 2.30-2.45 (1H, m), 2.60-2.80 (2H, m), 3.45-3.60 (1H, m), 4.50 (1H, d, $J=11.5$ Hz), 4.61 (1H, d, $J=11.5$ Hz), 7.25-7.40 (5H, m)

Reference Example 30

6-(3-Chloropropoxy)carbostyryl (5 g) and 1-amino-2-propanol (24 ml) are
10 dissolved in 2-propanol (100 ml), and the mixture is refluxed for 4 hours. After the reaction mixture is allowed to cool, the precipitated crystals are collected by filtration, washed with ethanol, and dried to give 6-[3-(2-hydroxypropyl)amino-propoxy]carbostyryl (3.1 g) as a white powder.

$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 1.03 (3H, d, $J=6$ Hz), 1.80-1.90 (2H, m), 2.40-
15 2.43 (2H, m), 2.66 (2H, t, $J=6.5$ Hz), 3.60-3.70 (1H, m), 4.04 (2H, t, $J=6.5$ Hz), 4.40-4.50 (1H, m), 6.48 (1H, d, $J=9.5$ Hz), 7.11-7.25 (3H, m), 7.83 (1H, d, $J=9.5$ Hz)

Reference Example 31

A solution of 6-(3-chloropropoxy)carbostyryl (5.0 g) and 3-amino-1-
20 propanol (24 ml) in methanol (25 ml) is heated at 100°C for 4 hours in an autoclave. The mixture is concentrated under reduced pressure to remove the solvent, and the residue is purified by silica gel column chromatography (solvent; methylene chloride:methanol:aqueous ammonia = 70:10:1), and recrystallized from methanol-diethyl ether to give 6-[3-(3-hydroxypropyl)amino-

propoxy]carbostyryl(4.4 g) as a white powder.

$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 1.45-1.65 (2H, m), 1.80-1.95 (2H, m), 2.40-2.75 (4H, m), 3.46 (2H, t, $J=6.5$ Hz), 4.03 (2H, t, $J=6.5$ Hz), 6.48 (1H, d, $J=9.5$ Hz), 7.10-7.30 (3H, m), 7.83 (1H, d, $J=9.5$ Hz)

5 Reference Example 32

The corresponding starting compounds are treated in the same manner as in Reference Example 1 to give the following compounds.

(1) 6-(3-Phthalimidopropoxy)-8-fluoro-3,4-dihydrocarbostyryl

Pale yellow powder

10 $^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 2.03 (2H, quint, $J=6$ Hz), 2.36-2.48 (2H, m), 2.70-2.90 (2H, m), 3.75 (2H, t, $J=6.5$ Hz), 3.97 (2H, t, $J=6$ Hz), 6.47 (1H, br-s), 6.55 (1H, dd, $J=2.5, 12$ Hz), 7.74-7.96 (4H, m), 9.91 (1H, s)

(2) 6-(3-Phthalimidopropoxy)-8-methoxycarbostyryl

Pale yellow powder

15 $^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 2.02-2.15 (2H, m), 3.77 (3H, s), 3.79 (2H, t, $J=6.5$ Hz), 4.04 (2H, t, $J=5.5$ Hz), 6.48 (1H, s), 6.49 (1H, d, $J=9.5$ Hz), 6.69 (1H, d, $J=2$ Hz), 7.77 (1H, d, $J=9.5$ Hz), 7.85-7.86 (5H, m), 7.80-7.90 (5H, m)

Reference Example 33

20 The corresponding starting compounds are treated in the same manner as in Reference Example 3 to give the following compounds.

(1) 6-[3-(1-Imidazolyl)carbonylaminopropoxy]-8-fluoro-3,4-dihydrocarbostyryl

White powder

$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 1.97 (2H, quint, $J=6$ Hz), 2.38-2.51 (2H, m), 2.82-2.96 (2H, m), 3.33-3.47 (2H, m), 4.01 (2H, t, $J=6.5$ Hz), 6.66 (1H, s), 6.71 (1H, dd, $J=2.5, 12.5$ Hz), 7.03 (1H, s), 7.66 (1H, s), 8.23 (1H, s), 8.57 (1H, t, $J=5.5$ Hz), 9.93 (1H, s)

- 5 (2) 6-[3-(1-Imidazolyl)carbonylaminopropoxy]-8-fluorocarbostyryl

White powder

$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 2.02 (2H, quint, $J=6$ Hz), 3.35-3.50 (2H, m), 4.10 (2H, t, $J=6$ Hz), 6.57 (1H, d, $J=9.5$ Hz), 7.03 (1H, s), 7.05-7.23 (2H, m), 7.67 (1H, s), 7.85 (1H, dd, $J=1.5, 10$ Hz), 8.24 (1H, s), 8.59 (1H, t, $J=5.5$ Hz), 11.67 (1H,

10 br-s)

- (3) 6-[3-(1-Imidazolyl)carbonylaminopropoxy]-8-methoxycarbostyryl

Pale yellow powder

$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 2.00-2.05 (2H, m), 3.44 (2H, t, $J=6$ Hz), 3.86 (3H, s), 4.08 (2H, t, $J=6$ Hz), 6.50 (1H, d, $J=9.5$ Hz), 6.74 (1H, d, $J=2$ Hz), 6.78 (1H, d, $J=2$ Hz), 7.03 (1H, s), 7.67 (1H, s), 7.79 (1H, d, $J=9.5$ Hz), 8.24 (1H, s), 8.55-8.65 (1H, m)

15

- (4) 6-[2-(1-Imidazolyl)carbonylaminoethoxy]carbostyryl

White powder

$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 3.60-3.72 (2H, m), 4.17 (2H, t, $J=5.5$ Hz), 6.49 (1H, d, $J=9.5$ Hz), 7.03 (1H, s), 7.15-7.30 (3H, m), 7.69 (1H, s), 7.82 (1H, d, $J=9.5$ Hz), 8.26 (1H, s), 8.70-8.85 (1H, m)

20

- (5) 6-[4-(1-Imidazolyl)carbonylaminobutoxy]carbostyryl

White powder

$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 1.62-1.90 (4H, m), 3.25-3.50 (2H, m), 4.03 (2H, t, $J=6$ Hz), 6.49 (1H, d, $J=9.5$ Hz), 7.03 (1H, s), 7.10-7.30 (3H, m), 7.67 (1H, s), 7.82 (1H, d, $J=9.5$ Hz), 8.24 (1H, s), 8.48-8.60 (1H, m), 11.65 (1H, br-s)

Reference Example 34

5 The corresponding starting compounds are treated in the same manner as in Reference Example 4 to give the following compounds.

(1) 6-(3-Chloropropoxy)-8-fluoro-3,4-dihydrocarbostyryl

White powder

10 $^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 2.22 (2H, quint, $J=6$ Hz), 2.64 (2H, t, $J=6$ Hz), 2.97 (2H, t, $J=6$ Hz), 3.73 (2H, t, $J=6$ Hz), 4.06 (2H, t, $J=6$ Hz), 6.50-6.63 (2H, m), 7.67 (1H, br-s)

(2) 6-(3-Chloropropoxy)-8-fluorocarbostyryl

Pale yellow powder

15 $^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 2.18 (2H, quint, $J=6$ Hz), 3.80 (2H, t, $J=6.5$ Hz), 4.13 (2H, t, $J=6$ Hz), 6.57 (1H, d, $J=10$ Hz), 7.07-7.23 (2H, m), 7.87 (1H, dd, $J=1.5, 10$ Hz), 11.65 (1H, br-s)

(3) 6-(2-Bromoethoxy)carbostyryl

White powder

20 $^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 3.81 (2H, t, $J=5.5$ Hz), 4.34 (2H, t, $J=5.5$ Hz), 6.49 (1H, d, $J=9.5$ Hz), 7.14-7.30 (3H, m), 7.82 (1H, d, $J=9.5$ Hz), 11.61 (1H, br-s)

(4) 6-(4-Bromobutoxy)carbostyryl

White powder

$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 1.75-2.10 (4H, m), 3.62 (2H, t, $J=6.5$ Hz),

4.02 (2H, t, J=6 Hz), 6.50 (1H, d, J=9.5 Hz), 7.10-7.35 (3H, m), 7.84 (1H, d, J=9.5 Hz), 11.66 (1H, br-s)

Reference Example 35

5 The corresponding starting compounds are treated in the same manner as in Reference Example 5 to give the following compounds.

(1) 6-(3-Phthalimidopropoxy)-8-fluorocarbostyryl

Pale yellow powder

¹H-NMR (DMSO-d₆) δ ppm: 2.08 (2H, quint, J=6 Hz), 3.78 (2H, t, J=6.5 Hz), 4.06 (2H, t, J=6 Hz), 6.55 (1H, d, J=9.5 Hz), 6.91 (1H, dd, J=2.5, 12 Hz), 6.98
10 (1H, br-s), 7.76-7.96 (4H, m), 11.60 (1H, br-s)

(2) 6-(2-Phthalimidoethoxy)carbostyryl

White powder

¹H-NMR (DMSO-d₆) δ ppm: 3.99 (2H, t, J=5.5 Hz), 4.25 (2H, t, J=5.5 Hz),
6.47 (1H, d, J=10 Hz), 7.10-7.30 (3H, m), 7.75-7.79 (5H, m)

15 (3) 6-(4-Phthalimidobutoxy)carbostyryl

Pale yellow powder

¹H-NMR (DMSO-d₆) δ ppm: 1.67-1.90 (4H, m), 3.55-3.76 (2H, m), 3.91-
4.16 (2H, m), 6.48 (1H, d, J=9.5 Hz), 7.08-7.32 (3H, m), 7.76-7.95 (5H, m)

Reference Example 36

20 The corresponding starting compounds are treated in the same manner as in Reference Example 2 to give the following compounds.

(1) 6-(3-Aminopropoxy)-8-fluorocarbostyryl hydrochloride

White powder

$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 2.06 (2H, quint, $J=6$ Hz), 2.87-3.10 (2H, m), 4.12 (2H, t, $J=6$ Hz), 6.57 (1H, d, $J=9.5$ Hz), 7.07-7.26 (2H, m), 8.88 (1H, br-d, $J=10$ Hz), 8.05-8.45 (3H, m), 11.40-11.88 (1H, m)

(2) 6-(3-Aminopropoxy)-8-methoxycarbostryl hydrochloride

5 Pale yellow powder

$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 2.04-2.10 (2H, m), 2.96 (2H, t, $J=6.5$ Hz), 4.10 (2H, t, $J=6$ Hz), 6.55 (1H, d, $J=9.5$ Hz), 6.81-6.84 (2H, m), 7.85 (1H, d, $J=9.5$ Hz), 8.10-8.35 (3H, m)

(3) 6-(2-Aminoethoxy)carbostryl

10 White powder

$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 2.88 (2H, t, $J=5.5$ Hz), 3.93 (2H, t, $J=5.5$ Hz), 6.48 (1H, d, $J=9.5$ Hz), 7.11-7.25 (3H, m), 7.83 (1H, d, $J=9.5$ Hz)

(4) 6-(4-Aminobutoxy)carbostryl

Pale yellow powder

15 $^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 1.67-1.97 (4H, m), 2.83 (2H, t, $J=6.5$ Hz), 4.01 (2H, t, $J=6$ Hz), 6.50 (1H, d, $J=9.5$ Hz), 7.10-7.37 (3H, m), 7.84 (1H, d, $J=9.5$ Hz)

Reference Example 37

To a solution of N-methylcyclohexylamine (17 g) in a 6N aqueous
20 hydrochloric acid solution (90 ml) is added dropwise an aqueous solution (60 ml) of sodium nitrite (20.7 g) at 60°C. The mixture is stirred at the same temperature for 2 hours, and diluted with methanol (300 ml). To the mixture are added an aqueous solution (100 ml) of sodium hydroxide (45 g) and

formamidine sulfinic acid (39 g). The mixture is refluxed for 2 hours, and diluted with water (400 ml). The mixture is extracted three times with methylene chloride, and the extract is washed with a saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated under
5 reduced pressure to remove the solvent. The residue is distilled under reduced pressure to give 1-methyl-1-cyclohexylhydrazine (10 g) as a colorless oil.

B.p. 76-78°C/19 mmHg

The corresponding starting compounds are treated in the same manner as in Reference Example 37 to give the following compound.

10 1-Cyclopropyl-1-cyclohexylhydrazine

Pale yellow oil

¹H-NMR (CDCl₃) δ ppm: 0.46-0.60 (4H, m), 1.01-1.43 (5H, m), 1.56-1.70 (1H, m), 1.73-1.85 (2H, m), 1.81-2.08 (3H, m), 2.43-2.58 (1H, m), 3.06 (2H, br-s)

Reference Example 38

15 To a solution of N-(trans-2-hydroxycyclohexyl)-N-cyclopropylamine (20 g) in methyl ethyl ketone (260 ml) is added with stirring a solution of D-di-p-toluoyltartaric acid (49.8 g) in methyl ethyl ketone (200 ml) at room temperature. The mixture is stirred at room temperature for 1.5 hour, and the precipitated crystals are collected by filtration, and washed successively with
20 methyl ethyl ketone and acetone. The crystals thus obtained are recrystallized from methanol-acetonitrile to give (R,R)-(-)-trans-N-(2-hydroxycyclohexyl)-N-cyclopropylamine D-di-p-toluoyltartrate (22.0 g) as a white powder.

M.p. 165°C

Reference Example 39

To an aqueous solution (80 ml) of sodium hydroxide (4 g) is added with stirring (R,R)-(-)-trans-N-(2-hydroxycyclohexyl)-N-cyclopropylamine D-di-p-toluoyletartrate (20 g) at room temperature. The mixture is further stirred at room
5 temperature for 0.5 hour, and extracted twice with ethyl acetate (40 ml). To the aqueous layer is added water (40 ml), and the mixture is further extracted three times with methylene chloride (20 ml). The organic layers are combined, and dried over anhydrous magnesium sulfate. The resultant is concentrated under reduced pressure to remove the solvent to give (R,R)-(-)-trans-N-(2-hydroxy-
10 cyclohexyl)-N-cyclopropylamine (5.2 g) as colorless rods.

M.p. 43-45°C

$[\alpha]_D^{24} = -59.3^\circ$ (c=1.0, methanol)

Reference Example 40

To a mixture of water (50 ml) and acetonitrile (50 ml) are added 6-(3-
15 aminopropoxy)carbostyryl hydrochloride (5.0 g) and potassium carbonate (3.4 g) at room temperature. The mixture is stirred at room temperature for 2 hours, and cooled to -5°C. To the mixture is added dropwise phenyl chlorocarbonate (3.9 g) while the temperature of the mixture is kept below 0°C. The mixture is stirred at the same temperature for 1 hour, and thereto is added water (100 ml),
20 and then the mixture is further stirred for 0.5 hour. The precipitated crystals are collected by filtration, and washed successively with water and acetone to give 6-(3-phenoxy-carbonylaminopropoxy)carbostyryl (6.0 g) as a white powder.

$^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 1.95 (2H, quint, $J=6.5$ Hz), 3.20-3.35 (2H, m), 4.06 (2H, t, $J=6.0$ Hz), 6.50 (1H, d, $J=9.5$ Hz), 7.05-7.40 (8H, m), 7.75-7.95

(2H, m), 11.65 (1H, br-s)

Example 1

6-[3-(1-Imidazolyl)carbonylaminopropoxy]carbostyryl (100 g) and trans-N-(2-hydroxycyclohexyl)-N-cyclopropylamine (49.6 g) are suspended in
5 chloroform (1 liter), and the mixture is refluxed for 10 hours. The insoluble materials are removed by filtration on celite, and the filtrate is washed successively with water and a saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to remove the solvent. The residue is purified by silica gel column chromatography (solvent; methylene chloride:ethyl acetate:methanol = 10:10:1), and
10 recrystallized from ethanol to give 6-{3-[3-(trans-2-hydroxycyclohexyl)-3-cyclopropylureido]propoxy}carbostyryl (83 g) as a white powder.

M.p. 163.5-164.5°C

Using the corresponding starting compounds, the compounds of
15 Examples 7-31 are obtained in the same manner as in Example 1.

Example 2

To a solution of 6-{3-[N-(trans-2-hydroxycyclohexyl)-N-cyclopropylamino]carbonylaminopropoxy}carbostyryl (5 g), triethylamine (4.2 ml) and 4-dimethylaminopyridine (0.48 g) in methylene chloride (100 ml) is added
20 dropwise with stirring acetic anhydride (3.17 ml) at room temperature. The mixture is stirred at room temperature for 2 hours, and thereto is added a 25 % aqueous ammonia (20 ml), and the mixture is stirred for 1 hour. The organic layer is separated, washed successively with water and a saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated under

reduced pressure to remove the solvent. The residue is purified by silica gel column chromatography (solvent; methylene chloride:methanol = 20:1), and recrystallized from ethanol-diethyl ether to give 6-{3-[3-(trans-2-acetyloxy-cyclohexyl)-3-cyclopropylureide]propoxy}carbostyryl (4.28 g) as a white powder.

M.p. 180-183°C

Using the corresponding starting compounds, the compounds of Examples 11 and 14 are obtained in the same manner as in Example 2.

Example 3

6-(3-Methylaminopropoxy)carbostyryl (3 g) is dissolved in dimethylformamide (150 ml), and thereto are added N-methyl-N-cyclohexylamino-carbonyl chloride (2.3 g) and potassium carbonate (2 g). The mixture is stirred at room temperature overnight, and further heated with stirring at 80°C for 2 hours. The reaction solution is poured into water, and extracted with ethyl acetate. The extract is concentrated under reduced pressure to remove the solvent, and the residue is purified by silica gel column chromatography (solvent; methylene chloride:methanol = 30:1), and recrystallized from ethyl acetate to give 6-[3-(1,3-dimethyl-3-cyclohexylureido)propoxy]carbostyryl (2.3 g) as a white powder.

M.p. 113-114°C

Example 4

To acetic acid (100 ml) is added 2-chloro-6-{3-[1-methyl-3-cyclohexyl-3-(2-acetyloxybutyl)ureido]propoxy}quinoline (5.5 g), and the mixture is refluxed for 4 hours. The mixture is concentrated under reduced pressure to

remove the acetic acid, and the residue is dissolved in methylene chloride and washed with a saturated aqueous sodium hydrogen carbonate solution. The mixture is dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to remove the solvent. The residue is purified by silica gel
5 column chromatography (solvent; methylene chloride:methanol = 20:1), and recrystallized from methylene chloride-diethyl ether to give 6-{3-[1-methyl-3-cyclohexyl-3-(2-acetyloxybutyl)ureido]propoxy}carbostyryl (2.7 g) as a white powder.

M.p. 164-166°C

10 Example 5

6-{3-[1-Methyl-3-cyclohexyl-3-(2-acetyloxybutyl)ureido]propoxy}-carbostyryl (1.63 g) is added to methanol (10 ml), and thereto is added dropwise a 10 % aqueous potassium hydroxide solution (10 ml). The mixture is stirred at room temperature overnight, and concentrated under reduced pressure to
15 remove the solvent. The resultant is poured into water, and extracted with chloroform. The extract is concentrated under reduced pressure to remove the solvent, and the residue is purified by silica gel column chromatography (solvent; methylene chloride:methanol = 20:1), and recrystallized from methylene chloride-diethyl ether to give 6-{3-[1-methyl-3-cyclohexyl-3-(2-
20 hydroxybutyl)ureido]propoxy}carbostyryl (0.6 g) as a white powder.

M.p. 173-175°C

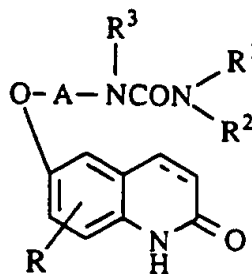
Using the corresponding starting compounds, the compounds of Examples 6 and 8-10 disclosed hereinafter are obtained in the same manner as in Example 5.

Examples 6 to 31

Using the corresponding starting compounds, the compounds as listed in Table 1 are obtained in the same manner as in Example 3 or 4.

Table 1

5

**Example 6**A: $-(CH_2)_3-$

R: H

R¹: R²: R³: H

Racemic compound

Bond between 3- and 4-positions of the carbostyryl nucleus: Double
 M.p. 163.5-164.5°C Crystalline form: White powder Form: Free
 Solvent for recrystallization: Ethanol

Example 7A: $-(CH_2)_3-$

R: H

R¹: R²: R³: H

Racemic compound

Bond between 3- and 4-positions of the carbostyryl nucleus: Double
 M.p. 180-183°C Crystalline form: White powder Form: Free
 Solvent for recrystallization: Ethanol-diethyl ether

Example 8

A: $-(CH_2)_3-$

R: H

R³: H

(S,S)-(+)-isomer

Bond between 3- and 4-positions of the carbostyryl nucleus: Double

M.p. 157-159°C

Crystalline form: White powder Form: Free

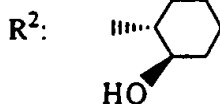
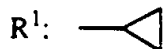
Solvent for recrystallization: Ethanol

 $[\alpha]_D^{24} = +1.4^\circ$ (c=1.0, methanol)

Example 9

A: $-(CH_2)_3-$

R: H

R³: H

(R,R)-(-)-isomer

Bond between 3- and 4-positions of the carbostyryl nucleus: Double

M.p. 158.5-160°C

Crystalline form: White powder Form: Free

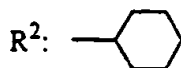
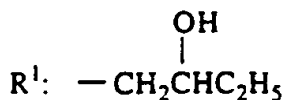
Solvent for recrystallization: Ethanol

 $[\alpha]_D^{24} = -1.3^\circ$ (c=1.0, methanol)

Example 10

A: $-(CH_2)_3-$

R: H

R³: H

Bond between 3- and 4-positions of the carbostyryl nucleus: Double

M.p. 104-111°C

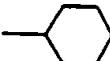
Crystalline form: White powder Form: Free

Solvent for recrystallization: Ethanol-water

Example 11

A: $-(CH_2)_3-$

R: H

$$R^1: -CH_2\overset{\overset{OCOCH_3}{|}}{CH}C_2H_5$$
R²: R³: H

Bond between 3- and 4-positions of the carbostyryl nucleus: Double

M.p. 165-167°C

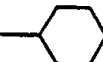
Crystalline form: White powder Form: Free

Solvent for recrystallization: Ethanol

Example 12

A: $-(CH_2)_3-$

R: H

R¹: $-CH_3$ R²: R³: $-CH_3$

Bond between 3- and 4-positions of the carbostyryl nucleus: Double

M.p. 113-114°C


Crystalline form: White powder Form: Free

Solvent for recrystallization: Ethyl acetate

Example 13

A: $-(CH_2)_3-$

R: H

$$R^1: -CH_2\overset{\overset{OH}{|}}{CH}C_2H_5$$
R²: R³: $-CH_3$

Bond between 3- and 4-positions of the carbostyryl nucleus: Double

M.p. 173-175°C


Crystalline form: White powder Form: Free

Solvent for recrystallization: Methylene chloride-diethyl ether

Example 14

A: $-(CH_2)_3-$

R: H

 $R^1: -CH_2\overset{\overset{OCOCH_3}{|}}{CH}C_2H_5$ $R^2: -$  $R^3: -CH_3$

Bond between 3- and 4-positions of the carbostyryl nucleus: Double

M.p. 164-166°C


Crystalline form: White powder Form: Free

Solvent for recrystallization: Methylene chloride-diethyl ether

Example 15

A: $-(CH_2)_3-$

R: H

 $R^1: -CH_3$ $R^2: -$  $R^3: -C_2H_5$

Bond between 3- and 4-positions of the carbostyryl nucleus: Double


M.p. 136-137°C

Form: Free

Example 16

A: $-(CH_2)_3-$

R: H

 $R^1: -CH_3$ $R^2: -$  $R^3: -CH_2CH=CH_2$

Bond between 3- and 4-positions of the carbostyryl nucleus: Double


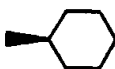
M.p. 116-117°C

Form: Free

Example 17

A: $-(CH_2)_3-$

R: H

R¹: R²: R³: HO(CH₂)₃OH

(R,R)-(-)-isomer

Bond between 3- and 4-positions of the carbostyryl nucleus: Double

M.p. 105-108°C

Crystalline form: White powder Form: Free

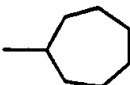
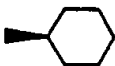
Solvent for recrystallization: Dichloromethane-diethyl ether

 $[\alpha]_D^{21} = -21.9^\circ$ (c=1.00, methanol)

Example 18

A: $-(CH_2)_3-$

R: H

R¹: R²: R³: H

HO

Racemic compound

Bond between 3- and 4-positions of the carbostyryl nucleus: Double

M.p. 105-106°C

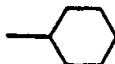
Crystalline form: White powder Form: Free

Solvent for recrystallization: Ethanol

Example 19

A: $-(CH_2)_3-$

R: H

R¹: $-\text{CH}_2\text{CH}(\text{OC}_2\text{H}_5)\text{C}_2\text{H}_5$ R²: R³: H

Bond between 3- and 4-positions of the carbostyryl nucleus: Double

M.p. 122-125°C

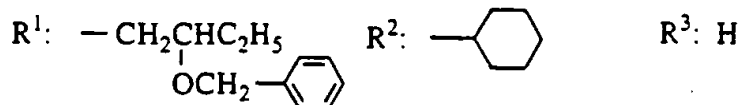
Crystalline form: White powder Form: Free

Solvent for recrystallization: Ethanol-diethyl ether

Example 20

A: $-(CH_2)_3-$

R: H



Bond between 3- and 4-positions of the carbostyryl nucleus: Double

M.p. 121-123°C

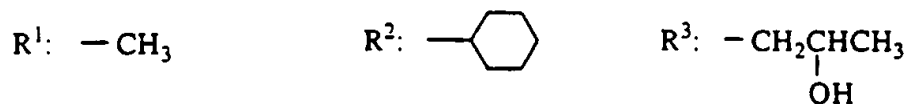
Crystalline form: White powder Form: Free

Solvent for recrystallization: n-Hexane

Example 21

A: $-(CH_2)_3-$

R: H



Bond between 3- and 4-positions of the carbostyryl nucleus: Double

M.p. 127-129°C

Crystalline form: White powder Form: Free

Solvent for recrystallization: Dichloromethane-ethyl acetate-methanol

Example 22

A: $-(CH_2)_3-$

R: H



Bond between 3- and 4-positions of the carbostyryl nucleus: Double

M.p. 141-142°C

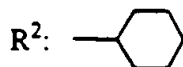
Crystalline form: White powder Form: Free

Solvent for recrystallization: Ethanol

Example 23

A: $-(CH_2)_3-$

R: H

R¹: $-CH_3$ R³: $-CH_2CH_2CH_3$

Bond between 3- and 4-positions of the carbostyryl nucleus: Double

M.p. 119-119.5°C

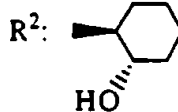
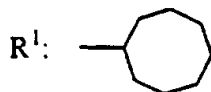
Crystalline form: Colorless flakes Form: Free

Solvent for recrystallization: Ethanol-diethyl ether

Example 24

A: $-(CH_2)_3-$

R: H

R³: H

Racemic compound

Bond between 3- and 4-positions of the carbostyryl nucleus: Double

M.p. 110-114°C

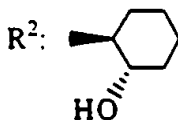
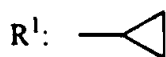
Crystalline form: White powder Form: Free

Solvent for recrystallization: Ethanol

Example 25

A: $-(CH_2)_3-$

R: 8-F

R³: H

Racemic compound

Bond between 3- and 4-positions of the carbostyryl nucleus: Single

M.p. 142-143°C

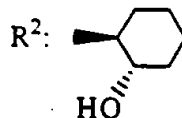
Crystalline form: White powder Form: Free

Solvent for recrystallization: Dichloromethane-diethyl ether

Example 26

A: $-(CH_2)_3-$

R: 8-F

R³: H

Racemic compound

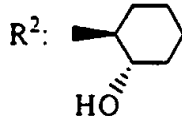
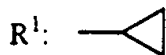
Bond between 3- and 4-positions of the carbostyryl nucleus: Double

M.p. 186-189°C

Crystalline form: White powder Form: Free

Solvent for recrystallization: Ethanol

Example 27

A: $-(CH_2)_3-$ R: 8-OCH₃R³: H

Racemic compound

Bond between 3- and 4-positions of the carbostyryl nucleus: Double

M.p. 161-162°C

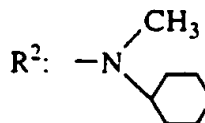
Crystalline form: White powder Form: Free

Solvent for recrystallization: Ethanol

Example 28

A: $-(CH_2)_3-$

R: H

R¹: HR³: H

Bond between 3- and 4-positions of the carbostyryl nucleus: Double

M.p. 169-171°C

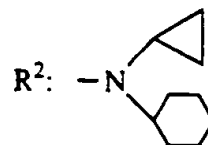
Crystalline form: White powder Form: Free

Solvent for recrystallization: Ethanol-diethyl ether

Example 29

A: $-(CH_2)_3-$

R: H

R¹: HR³: H

Bond between 3- and 4-positions of the carbostyryl nucleus: Double

M.p. 187-188.5°C

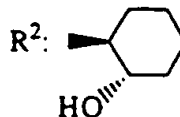
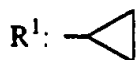
Crystalline form: White powder Form: Free

Solvent for recrystallization: Ethanol

Example 30

A: $-(CH_2)_2-$

R: H

R³: H

Racemic compound

Bond between 3- and 4-positions of the carbostyryl nucleus: Double

M.p. 163-165°C

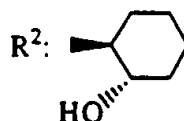
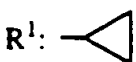
Crystalline form: White powder Form: Free

Solvent for recrystallization: Ethanol

Example 31

A: $-(CH_2)_4-$

R: H

R³: H

(R,R)-(-)-isomer

Bond between 3- and 4-positions of the carbostyryl nucleus: Double

M.p. 94-97°C

Crystalline form: White powder Form: Free

Solvent for recrystallization: Ethanol

 $[\alpha]_D^{25} = -1.0^\circ$ (c=1.0, methanol)

Example 32

(R,R)-(-)-6-{3-[3-[trans-2-[3-(2-Tetrahydropyranyloxy)propoxy]cyclohexyl]-3-cyclopropylureido]propoxy}-2-methoxymethoxyquinoline (1.7 g) is dissolved in ethanol (17 ml), and thereto is added dropwise with stirring a 2N
5 hydrochloric acid (17 ml) at room temperature. The mixture is stirred at room temperature for 2 hours, and concentrated under reduced pressure to remove the ethanol. The residue is purified by silica gel column chromatography (solvent; ethyl acetate:n-hexane = 1:1), and recrystallized from methylene chloride-diethyl ether to give (R,R)-(-)-6-{3-[3-[trans-2-(3-hydroxypropoxy)-
10 cyclohexyl]-3-cyclopropylureido]propoxy}carbostyryl (1.2 g) as a white powder.

M.p. 105-108°C

$[\alpha]_D^{21} = -21.9^\circ$ (c=1.00, methanol)

Example 33

15 6-[3-(3-Cyclohexyl-3-methyl-1-allylureido)propoxy]carbostyryl (3.0 g) is dissolved in ethanol (90 ml), and thereto is added 10 % palladium-carbon (0.3 g), and the mixture is subjected to catalytic hydrogenation under 1 atm of hydrogen gas at room temperature. After the reaction is complete, the catalyst is removed by filtration, and the filtrate is concentrated under reduced pressure.
20 The residue is purified by silica gel column chromatography (solvent; methylene chloride:methanol = 20:1), and recrystallized from ethanol-diethyl ether to give 6-[3-(3-cyclohexyl-3-methyl-1-propylureido)propoxy]carbostyryl (2.1 g) as colorless flakes.

M.p. 119-119.5°C

The corresponding starting compounds are treated in the same manner as in Example 33 to give the compound of Example 15.

Example 34

To a mixture of dimethylformamide (45 ml) and water (5 ml) are added 6-
5 (3-phenoxy-carbonylaminopropoxy)carbostyryl (5.0 g) and (R,R)-(-)-N-(trans-2-hydroxycyclohexyl)-N-cyclopropylamine (2.4 g), and the mixture is heated with stirring at 85°C for 6 hours. To the mixture is added water (80 ml) at 80°C, and the mixture is allowed to cool while the mixture is stirred overnight. The precipitated crystals are collected by filtration, washed with water, and purified
10 by silica gel column chromatography (solvent; methylene chloride:methanol:ethyl acetate = 5:1:5), and recrystallized from ethanol to give (R,R)-(-)-6-{3-[3-(trans-2-hydroxycyclohexyl)-3-cyclopropylureido]propoxy}carbostyryl (2.9 g) as a white powder.

M.p. 158.5-160°C

15 $[\alpha]_D^{24} = -1.3^\circ$ (c=1.0, methanol)

The corresponding starting compounds are treated in the same manner as in Example 34 to give the compounds of Examples 6-8 and 10-31.

Pharmacological Experiment 1 Platelet aggregation inhibitory activity

(1) Preparation of platelet rich plasma (PRP):

20 The blood was collected from the carotid of a male rabbit without anesthesia (NZW species, body weight; 2-3 kg) with mixing thereof with 1/10 volume of citric acid. The blood thus obtained was separated and put into plastic test tubes (each about 7 ml), and centrifuged at 900 rpm for 15 minutes at room temperature to give a turbid supernatant as a platelet rich plasma (PRP).

The residue from which PRP is separated was centrifuged at 3000 rpm for 10 minutes, and the supernatant was collected as a platelet poor plasma (PPP). The PRP was diluted with PPP so that the concentration thereof was adjusted to 5×10^5 cells/ μ l, and used in the platelet aggregation inhibitory activity test.

5 (2) Method for platelet aggregation inhibitory activity test:

The platelet aggregation was tested according to Born's turbidimetry. That is, a test compound was dissolved in dimethylformamide, and the test compound solution (1 μ l) thus obtained was put into a cuvette, and thereto was further added PRP (200 μ l). Immediately thereafter, the cuvette was set into an apparatus for determining platelet aggregation activity, PAM-8T (manufactured by Mevanix Inc.), and the mixture was incubated at 37°C. Precisely three minutes thereafter, a solution of adenosine diphosphate (ADP, PA test ADP [MCM], purchased by MC Medical Ltd.) in physiological saline solution or a collagen solution (Collagenreagent Horm, purchased by MC Medical Ltd.) (20 10 μ l) was added thereto. The final concentration of the ADP solution or the collagen solution was 7.5 μ M or 20 μ g/ml, respectively.

The maximum aggregation rate and the aggregation inhibitory rate were calculated by the following equations.

$$20 \quad \text{Maximum Aggregation Rate} = \frac{X - \text{Optical transmission of PRP}}{\text{Optical transmission of PPP} - \text{Optical transmission of PRP}} \times 100$$

X: Maximum optical transmission on the aggregation response curve

Aggregation
Inhibitory Rate =

$$\left(1 - \frac{\text{Maximum Aggregation Rate of PRP treated by a test compound}}{\text{Maximum Aggregation Rate of PRP treated by a solvent}} \right) \times 100$$

- 5 IC_{50} , which is a concentration of the test compound being required to inhibit the platelet aggregation reaction by 50%, was determined from the aggregation inhibitory rates at two different concentrations of a test compound. The results are shown in Table 2.

Table 2

Test Compound No.	ADP IC ₅₀ (μmole)	Collagen IC ₅₀ (μmole)
The compound of Ex. 6	1.8	1.9
The compound of Ex. 7	18.2	2.1
The compound of Ex. 8	2.1	2.0
The compound of Ex. 9	1.9	2.0
The compound of Ex. 10	0.4	0.3
The compound of Ex. 11	0.6	2.1
The compound of Ex. 12	31.6	20.5
The compound of Ex. 13	2.1	2.0
The compound of Ex. 14	1.5	2.2
The compound of Ex. 15	15.2	16.1
The compound of Ex. 16	4.6	20.0
The compound of Ex. 17	0.14	2.39
The compound of Ex. 18	0.12	0.03
The compound of Ex. 19	0.18	0.59
The compound of Ex. 20	0.22	0.29
The compound of Ex. 21	2.08	3.25
The compound of Ex. 22	1.31	2.80
The compound of Ex. 23	13.4	2.51
The compound of Ex. 24	0.08	0.03
The compound of Ex. 25	4.65	3.90
The compound of Ex. 26	0.45	3.03
The compound of Ex. 27	31.6	31.6
The compound of Ex. 28	0.11	0.10
The compound of Ex. 29	0.01	0.03
The compound of Ex. 30	3.67	2.94
The compound of Ex. 31	15.7	2.57

Pharmacological Experiment 2 Antithrombotic activity

Antithrombotic activity of the test compounds was estimated by an inhibitory activity of the test compound by oral administration against death induced by pulmonary infarction in mice which was introduced by intravenous administration of collagen (pulmonary infarction inhibitory activity).

Male ICR mice (5-week old, body weight; about 25 g) was fasted overnight, and separated into groups (15 mice per each group) and numbered. A test compound solution, which was prepared by suspending a test compound in 1 % hydroxypropylmethyl cellulose 2910 TC-5 (HPMC, manufactured by Shin-etsu Chemical Co., Ltd.), was orally administered to the mice, and 10 minutes thereafter, a collagen solution (the method for preparation thereof and a dose thereof are explained hereafter) was injected to the mice at the tail vein at the constant rate. The lethality of the mice was determined by the number of mice which were died in an hour after the administration of collagen solution.

The antithrombotic activity of the test compound was estimated by the inhibitory rate (%) of the lethality of the mice. The collagen solution was prepared by dissolving collagen (Type III, manufactured by Sigma Chemical Ltd.) in 0.05 M acetic acid solution containing 2 mM calcium chloride and 5 % glucose at 4°C so that the final concentration of collagen was adjusted to 2.5 mg/ml, and then the pH value thereof was adjusted to pH 7.4 with sodium hydroxide the day before the experiment. The collagen solution was incubated with stirring at 37°C for two hours, and then further stirred at room temperature overnight. Just before the experiment, the pH value of the collagen solution was adjusted again to pH 7.4. The amount of the collagen solution which was

injected at the tail vein was previously determined so that the lethality by pulmonary infarction induced thereby became about 75 %. The results are shown in Table 3.

100

Table 3

Test Compound No.	Pulmonary infarction inhibitory activity (%) 30 mg/kg
The compound of Ex. 6	100
The compound of Ex. 7	67
The compound of Ex. 8	100
The compound of Ex. 9	100
The compound of Ex. 10	74
The compound of Ex. 11	80
The compound of Ex. 12	100
The compound of Ex. 13	58
The compound of Ex. 14	66
The compound of Ex. 15	86
The compound of Ex. 16	77
The compound of Ex. 17	100
The compound of Ex. 18	69
The compound of Ex. 19	84
The compound of Ex. 20	66
The compound of Ex. 21	59
The compound of Ex. 22	69
The compound of Ex. 23	90
The compound of Ex. 24	100
The compound of Ex. 25	100
The compound of Ex. 26	85
The compound of Ex. 27	80
The compound of Ex. 28	100
The compound of Ex. 29	91
The compound of Ex. 30	100
The compound of Ex. 31	48

Pharmacological Experiment 3 Intima thickening inhibitory activity

Male SD rats (6-week old) were separated into groups (8 rats per each group) and numbered. A test compound solution, which was prepared by suspending a test compound in 1 % hydroxypropylmethyl cellulose 2910 TC-5 (HPMC, manufactured by Shin-etsu Chemical Co., Ltd.) was orally administered to the rats. In the control group, 1 % HPMC solution was orally administered instead of the test compound solution. One or two hours thereafter, two french balloon catheters (manufactured by Baxter Travenol Inc.) were inserted into the left common carotid artery of the rats, and the artery was injured by abrading five times with a balloon. The day of balloon abrasion was considered as Day 0. On the following day (Day 1), a test compound was orally administered to the rats two times a day (in the morning and in the evening). On Day 2, 1.48 MBq/ml of ^3H -thymidine (dose: 5 ml/kg, manufactured by NEN Research Products, Ltd.) was injected at the tail vein of the rats about one hour after the administration of the test compound so that the time after the balloon injury was fixed to the same in each rat. Precisely 45 minutes after the injection of ^3H -thymidine at the tail vein, the common carotid artery of the rats was taken out. In the test compound-treated group, only the left common carotid artery which was injured by balloon was taken out, and in the control group, both the left and right common carotid arteries were taken out. The common carotid artery thus obtained was cut to pieces of exact 1 cm long, and the unnecessary portions such as the outer membrane or the nerves were completely removed. The common carotid artery was put into a glass vial, and thereto was added a 0.5 N sodium hydroxide (0.5 ml), and the mixture was incubated at 37°C

overnight to be solubilized. The mixture was neutralized with a 5 N hydrochloric acid (0.05 ml), and thereto was further added an aqueous hydrogen peroxide solution (0.1 ml). Aquasol II (10 ml, manufactured by Du Pont Co.) was added thereto, and the mixture was well stirred and then allowed
5 to stand for 30 minutes. The radioactivity of tritium in the mixture was counted by liquid scintillation counter. The intima thickening inhibitory activity of the test compound was calculated by the following equation.

$$\text{Intima Thickening Inhibitory Rate (\%)} = \frac{L(c) - L}{L(c) - R(c)} \times 100$$

- 10 L (c): The amount of tritium in the left common carotid artery in the control group (dpm)
- R (c): The amount of tritium in the right common carotid artery in the control group (dpm)
- 15 L: The amount of tritium in the left common carotid artery in the test compound-treated group (dpm)

The results are shown in Table 4.

Table 4

Test Compound No.	Dose (mg/kg)	Intima thickening inhibitory activity (%)
The compound of Ex. 6	10	31.4
The compound of Ex. 7	30	15.2
The compound of Ex. 8	30	13.3
The compound of Ex. 9	10	26.8
The compound of Ex. 10	30	34.2
The compound of Ex. 11	30	33.0
The compound of Ex. 12	30	21.1
The compound of Ex. 13	30	16.6
The compound of Ex. 14	30	15.7
The compound of Ex. 15	30	11.9
The compound of Ex. 16	30	33.3
The compound of Ex. 17	30	16.0
The compound of Ex. 18	30	19.0
The compound of Ex. 19	30	23.4
The compound of Ex. 26	30	16.0
The compound of Ex. 28	30	27.8
The compound of Ex. 29	30	29.3

Pharmacological Experiment 4

cGMP-inhibited cAMP phosphodiesterase (PDE3) inhibitory activity

- 5 The PDE3 inhibitory activity of the present compounds was determined according to the method disclosed in *Biochemica et Biophysica Acta*, 429, pp. 485-497 (1976) and *Biochemical Medicine*, 10, pp. 301-311 (1974).

A PDE enzyme was a recombinant enzyme which was prepared by expressing in insect cell Sf9 by baculovirus expression system from cDNA of
 10 PDE3 (cf. *Diabetes*, 44, p. 67, (1995)). The cDNA was human myocardial cyclic-

GMP inhibited PDE (hcGIP2, reference; Proc. Natl. Acad. Sci. USA, 89, 3721, (1992), GenBank M91667).

The PDE activity was tested in a reaction mixture (200 μ l) of 50 mM Tris-HCl buffer (pH 8.0), 0.5 mM $MgCl_2$, 2 mM EGTA, 0.1 mg/ml BSA, 0.4 μ M [8-

5 3H]cAMP, a PDE enzyme and a test compound. The reaction mixture was incubated at 30°C for 15 minutes to make the PDE enzyme work, and then the reaction was quenched by incubating at 100°C for 6 minutes in order to inactivate the PDE enzyme. The reaction mixture was cooled, and added thereto snake venom so that the final concentration thereof was 0.1 mg/ml. The
10 mixture was incubated at 30°C for 10 minutes to generate [8- 3H] adenosine. The [8- 3H] adenosine thus obtained was isolated and collected by cation ion exchange column and the radioactivity thereof was determined by liquid scintillation counter.

The test compounds were dissolved in N,N-dimethylformamide (DMF),
15 and the test compound solution thus obtained was added to the reaction mixture so that the final concentration thereof in the reaction mixture was controlled to 0.5 %. Each assay was done in duplicate. The PDE activity (V_s) in the reaction mixture at each concentration of the test compound was estimated from the test results, and the PDE activity inhibitory activity (%) of
20 the test compound was calculated according to the following equation based on the PDE activity (V_c) in the control group wherein DMF was used instead of the test compound solution.

$$\text{PDE Activity Inhibitory Rate (\%)} = \frac{V_c - V_s}{V_c} \times 100$$

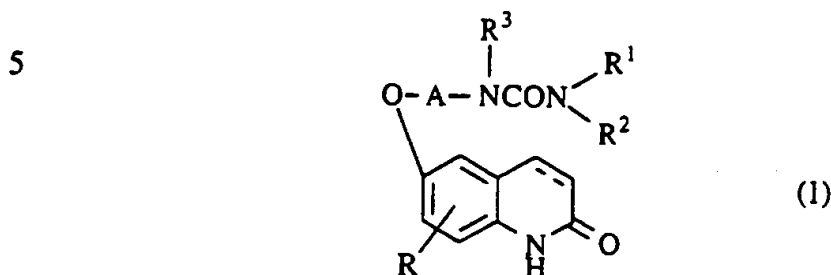
The PDE inhibitory activity was expressed by IC_{50} , which is a concentration of the test compound being required to inhibit the PDE activity by 50%. The results are shown in Table 5.

Table 5

Test Compound No.	PDE inhibitory activity IC_{50} (mole)
The compound of Ex. 8	1.13×10^{-7}
The compound of Ex. 9	9.30×10^{-8}
The compound of Ex. 10	2.43×10^{-8}
The compound of Ex. 12	1.97×10^{-7}
The compound of Ex. 17	6.08×10^{-8}
The compound of Ex. 24	6.47×10^{-10}
The compound of Ex. 26	7.46×10^{-8}
The compound of Ex. 27	2.18×10^{-6}
The compound of Ex. 28	8.26×10^{-10}

CLAIMS

1. A carbostyryl derivative of the formula (1):



wherein A is a lower alkylene group,

10 R is a hydrogen atom, a halogen atom or a lower alkoxy group,

R¹ and R² are the same or different and are each a lower alkyl group having optionally a substituent selected from a hydroxy group, a lower alkoxy group, a phenyl-lower alkoxy group and a lower alkanoyloxy group; a cycloalkyl group having optionally a substituent selected from a hydroxy group, a hydroxy-substituted lower alkoxy group and a lower alkanoyloxy group; or an amino group having optionally a substituent selected from a lower alkyl group and a cycloalkyl group,

15

R³ is a hydrogen atom, a lower alkyl group, a lower alkenyl group or a hydroxy-substituted lower alkyl group, and

20 the bond between 3- and 4-positions of the carbostyryl nucleus is a single bond or a double bond,

provided that when R and R³ are a hydrogen atom, R¹ and R² should not be either an unsubstituted lower alkyl group or an unsubstituted cycloalkyl group,

or a salt thereof.

2. The carbostyryl derivative according to claim 1, wherein R and R³ are a hydrogen atom, or a salt thereof.

3. The carbostyryl derivative according to claim 1, wherein R is a
5 hydrogen atom, and R³ is a lower alkyl group, a lower alkenyl group or a hydroxy-substituted lower alkyl group, or a salt thereof.

4. The carbostyryl derivative according to claim 1, wherein R is a halogen atom or a lower alkoxy group, and R³ is a hydrogen atom, or a salt thereof.

10 5. The carbostyryl derivative according to claim 1, wherein R is a halogen atom or a lower alkoxy group, and R³ is a lower alkyl group, a lower alkenyl group or a hydroxy-substituted lower alkyl group, or a salt thereof.

6. The carbostyryl derivative according to claim 2, wherein R¹ and R² are the same and are each a lower alkyl group having optionally a substituent
15 selected from a hydroxy group, a lower alkoxy group, a phenyl-lower alkoxy group and a lower alkanoyloxy group; a cycloalkyl group having optionally a substituent selected from a hydroxy group, a hydroxy-substituted lower alkoxy group and a lower alkanoyloxy group; or an amino group having optionally a substituent selected from a lower alkyl group and a cycloalkyl group, or a salt
20 thereof.

7. The carbostyryl derivative according to claim 2, wherein R¹ is a lower alkyl group having optionally a substituent selected from a hydroxy group, a lower alkoxy group, a phenyl-lower alkoxy group and a lower

alkanoyloxy group, and R^2 is a cycloalkyl group having optionally a substituent selected from a hydroxy group, a hydroxy-substituted lower alkoxy group and a lower alkanoyloxy group; or an amino group having optionally a substituent selected from a lower alkyl group and a cycloalkyl group, or a salt thereof.

8. The carbostyryl derivative according to claim 2, wherein R^1 is a cycloalkyl group having optionally a substituent selected from a hydroxy group, a hydroxy-substituted lower alkoxy group and a lower alkanoyloxy group, and R^2 is an amino group having optionally a substituent selected from a lower alkyl group and a cycloalkyl group, or a salt thereof.

9. The carbostyryl derivative according to claim 3, wherein R^1 and R^2 are the same and are each a lower alkyl group having optionally a substituent selected from a hydroxy group, a lower alkoxy group, a phenyl-lower alkoxy group and a lower alkanoyloxy group; a cycloalkyl group having optionally a substituent selected from a hydroxy group, a hydroxy-substituted lower alkoxy group and a lower alkanoyloxy group; or an amino group having optionally a substituent selected from a lower alkyl group and a cycloalkyl group, or a salt thereof.

10. The carbostyryl derivative according to claim 3, wherein R^1 is a lower alkyl group having optionally a substituent selected from a hydroxy group, a lower alkoxy group, a phenyl-lower alkoxy group and a lower alkanoyloxy group, and R^2 is a cycloalkyl group having optionally a substituent selected from a hydroxy group, a hydroxy-substituted lower alkoxy

group and a lower alkanoyloxy group; or an amino group having optionally a substituent selected from a lower alkyl group and a cycloalkyl group, or a salt thereof.

11. The carbostyryl derivative according to claim 3, wherein R¹ is a
5 cycloalkyl group having optionally a substituent selected from a hydroxy group, a hydroxy-substituted lower alkoxy group and a lower alkanoyloxy group, and R² is an amino group having optionally a substituent selected from a lower alkyl group and a cycloalkyl group, or a salt thereof.

12. The carbostyryl derivative according to claim 4, wherein R¹ and R²
10 are the same and are each a lower alkyl group having optionally a substituent selected from a hydroxy group, a lower alkoxy group, a phenyl-lower alkoxy group and a lower alkanoyloxy group; a cycloalkyl group having optionally a substituent selected from a hydroxy group, a hydroxy-substituted lower alkoxy group and a lower alkanoyloxy group; or an amino group having optionally a
15 substituent selected from a lower alkyl group and a cycloalkyl group, or a salt thereof.

13. The carbostyryl derivative according to claim 4, wherein R¹ is a
lower alkyl group having optionally a substituent selected from a hydroxy group, a lower alkoxy group, a phenyl-lower alkoxy group and a lower
20 alkanoyloxy group, and R² is a cycloalkyl group having optionally a substituent selected from a hydroxy group, a hydroxy-substituted lower alkoxy group and a lower alkanoyloxy group; or an amino group having optionally a substituent selected from a lower alkyl group and a cycloalkyl group, or a salt

thereof.

14. The carbostyryl derivative according to claim 4, wherein R¹ is a cycloalkyl group having optionally a substituent selected from a hydroxy group, a hydroxy-substituted lower alkoxy group and a lower alkanoyloxy group, and R² is an amino group having optionally a substituent selected from a lower alkyl group and a cycloalkyl group, or a salt thereof.

15. The carbostyryl derivative according to claim 5, wherein R¹ and R² are the same and are each a lower alkyl group having optionally a substituent selected from a hydroxy group, a lower alkoxy group, a phenyl-lower alkoxy group and a lower alkanoyloxy group; a cycloalkyl group having optionally a substituent selected from a hydroxy group, a hydroxy-substituted lower alkoxy group and a lower alkanoyloxy group; or an amino group having optionally a substituent selected from a lower alkyl group and a cycloalkyl group, or a salt thereof.

16. The carbostyryl derivative according to claim 5, wherein R¹ is a lower alkyl group having optionally a substituent selected from a hydroxy group, a lower alkoxy group, a phenyl-lower alkoxy group and a lower alkanoyloxy group, and R² is a cycloalkyl group having optionally a substituent selected from a hydroxy group, a hydroxy-substituted lower alkoxy group and a lower alkanoyloxy group; or an amino group having optionally a substituent selected from a lower alkyl group and a cycloalkyl group, or a salt thereof.

17. The carbostyryl derivative according to claim 5, wherein R¹ is a

cycloalkyl group having optionally a substituent selected from a hydroxy group, a hydroxy-substituted lower alkoxy group and a lower alkanoyloxy group, and R² is an amino group having optionally a substituent selected from a lower alkyl group and a cycloalkyl group, or a salt thereof.

5 18. The carbostyryl derivative according to any one of claims 6 to 17, wherein the bond between 3- and 4-positions of the carbostyryl nucleus is a single bond, or a salt thereof.

 19. The carbostyryl derivative according to any one of claims 6 to 17, wherein the bond between 3- and 4-positions of the carbostyryl nucleus is a
10 double bond, or a salt thereof.

 20. 6-{3-[3-(trans-2-Hydroxycyclohexyl)-3-cyclopropylureido]-propoxy}carbostyryl

 21. (S,S)-(+)-6-{3-[3-(2-Hydroxycyclohexyl)-3-cyclopropylureido]-propoxy}carbostyryl

15 22. (R,R)-(-)-6-{3-[3-(2-Hydroxycyclohexyl)-3-cyclopropylureido]-propoxy}carbostyryl

 23. 6-{3-[3-(2-Hydroxycyclobutyl)-3-cyclopropylureido]propoxy}-carbostyryl

 24. Antithrombotic agent which comprises as an active ingredient a
20 therapeutically effective amount of the compound as set forth in claim 1, or a salt thereof, in admixture with a conventional pharmaceutically acceptable carrier or diluent.

 25. An agent for inhibiting the intima thickening, which comprises as an active ingredient a therapeutically effective amount of the compound as set

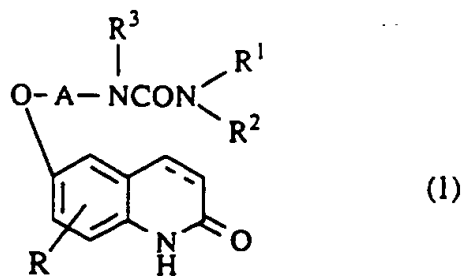
forth in claim 1, or a salt thereof, in admixture with a conventional pharmaceutically acceptable carrier or diluent.

26. A platelet aggregation inhibitor, which comprises as an active ingredient a therapeutically effective amount of the compound as set forth in claim 1, or a salt thereof, in admixture with a conventional pharmaceutically acceptable carrier or diluent.

27. An agent for dissociating the platelet mass, which comprises as an active ingredient a therapeutically effective amount of the compound as set forth in claim 1, or a salt thereof, in admixture with a conventional pharmaceutically acceptable carrier or diluent.

28. An agent for increasing the blood flow in the brain and the peripheral vessel, which comprises as an active ingredient a therapeutically effective amount of the compound as set forth in claim 1, or a salt thereof, in admixture with a conventional pharmaceutically acceptable carrier or diluent.

29. A process for preparing a carbostyryl derivative of the formula (1):



wherein A is a lower alkylene group,

R is a hydrogen atom, a halogen atom or a lower alkoxy group,

R¹ and R² are the same or different and are each a lower alkyl group having optionally a substituent selected from a hydroxy group, a lower alkoxy

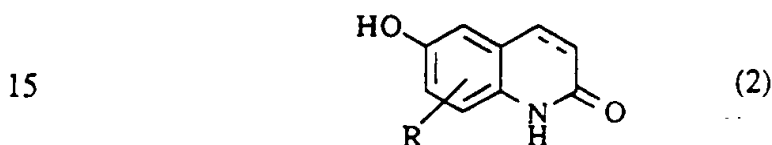
group, a phenyl-lower alkoxy group and a lower alkanoyloxy group; a cycloalkyl group having optionally a substituent selected from a hydroxy group, a hydroxy-substituted lower alkoxy group and a lower alkanoyloxy group; or an amino group having optionally a substituent selected from a lower alkyl group and a cycloalkyl group,

R^3 is a hydrogen atom, a lower alkyl group, a lower alkenyl group or a hydroxy-substituted lower alkyl group, and

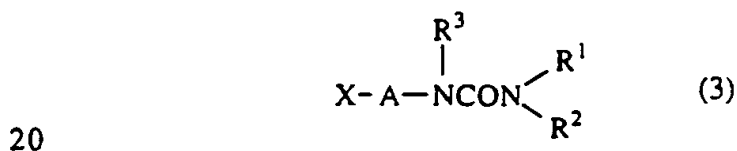
the bond between 3- and 4-positions of the carbostyryl nucleus is a single bond or a double bond,

provided that when R and R^3 are a hydrogen atom, R^1 and R^2 should not be either an unsubstituted lower alkyl group or an unsubstituted cycloalkyl group, or a salt thereof, which comprises

(i) reacting a compound of the formula (2):

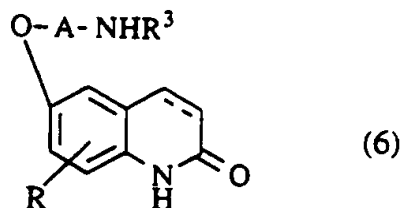


wherein R is the same as defined above, with a compound of the formula (3):

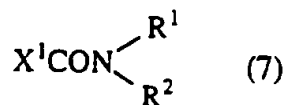


wherein A, R^1 , R^2 and R^3 are the same as defined above, and X is a halogen atom, a lower alkanesulfonyloxy group, an arylsulfonyloxy group or an aralkylsulfonyloxy group, in the presence of a basic compound, if necessary, followed by converting the product into a salt thereof, or

(ii) reacting a compound of the formula (6):

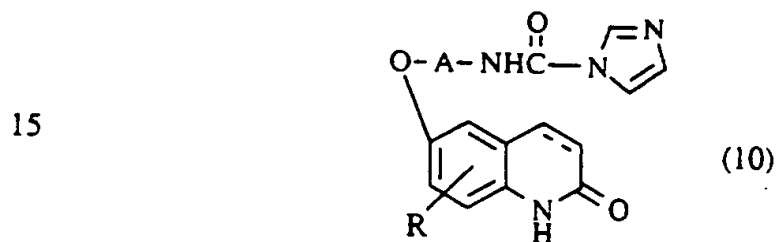


wherein A, R and R³ is the same as defined above, with a compound of the formula (7):

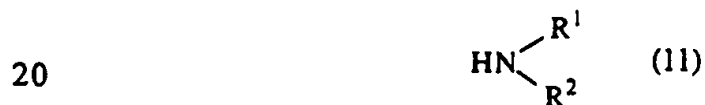


wherein R¹, R² are the same as defined above, and X¹ is a halogen atom, if necessary, followed by converting the product into a salt thereof, or

(iii) reacting a compound of the formula (10):



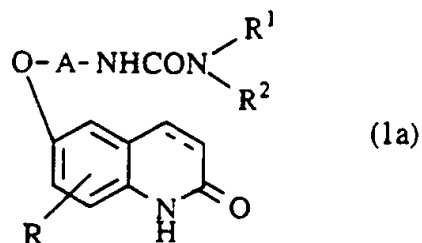
wherein A and R are the same as defined above, with a compound of the formula (11):



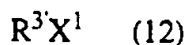
wherein R¹ and R² are the same as defined above, if necessary, followed by converting the product into a salt thereof, or

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(iv) reacting a compound of the formula (1a):

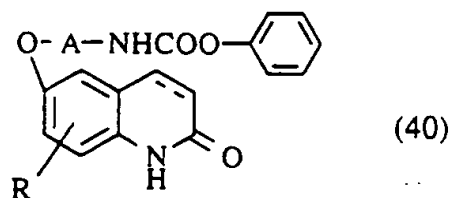


wherein A, R, R¹ and R² are the same as defined above, with a compound of the formula (12):

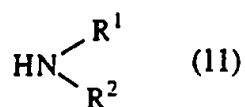


wherein X¹ is the same as defined above, and R³' is a lower alkyl group, a lower alkenyl group or a hydroxy-substituted lower alkyl group, if necessary, followed by converting the product into a salt thereof, or

(v) reacting a compound of the formula (40):



wherein A and R are the same as defined above, with a compound of the formula (11):



wherein R¹ and R² are the same as defined above, if necessary, followed by converting the product into a salt thereof.

INTERNATIONAL SEARCH REPORT

Intern: al Application No
PCT/JP 96/02892

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D215/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 569 592 A (OTSUKA PHARMACEUTICAL CO., LTD.) 18 November 1993 cited in the application * examples 11,131,133,139 * -----	1,24

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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Date of the actual completion of the international search

2 December 1996

Date of mailing of the international search report

10.12.96

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 96/02892

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		AU-A- 2429292	16-03-93
		CA-A- 2093633	24-02-93
		WO-A- 9304042	04-03-93
		JP-A- 5194405	03-08-93
		US-A- 5506239	09-04-96

Form PCT/ISA/210 (patent family annex) (July 1992)

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